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DEAGGLOMERATION OF DRY POWDER PHARMACEUTICAL AEROSOLS

by

Austin Paul Voss ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

Department of Mechanical Engineering

Edmonton, Alberta
[illegible]

"A Life spent making mistakes is not only more honorable
but is more useful than a life spent doing nothing."
George Bernard Shaw

University of Alberta

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Faculty of Graduate Studies and Research

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Deaggregation of Dry Powder Pharmaceutical Aerosols** submitted by Austin Paul Voss in partial fulfillment of the requirements for the degree of **Master of Science**.

To my brother Karl, my inspiration,
to my parents Lillian and Gary, my conscience,
and to Melanie, my unconditional support.

Acknowledgements

I would like to thank Dr. Warren Finlay for the guidance and support needed to complete this thesis. I would also like to acknowledge Dr. Carlos Lange, Helena Orszanska, Wes Dehaan, Anthony Roth and everyone in the aerosol research lab for their much needed help.

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Abstract

In this thesis, a rig is developed that tests the tendency of a dry powder aerosol formulation to deagglomerate, and the forces that deagglomerate it.

Turbulent deaggregation using a novel powder dispersion rig was tested using the powder from the Glaxo Ventodisks and compared to the Glaxo Diskhaler. These tests showed that although the turbulence from the rig was higher, the amount of deagglomerated powder from the Diskhaler was larger. From this information it seems that turbulence is not the only force in the inhaler that is deagglomerating the powder.

Mechanical impaction deaggregation was tested by the use of an obstructing mesh. The deaggregation found when using the mesh was similar to using no mesh, leading to the conclusion that the force caused by the impaction of the powder into the grid was not large enough to deagglomerate the powder.

Ventodisks were placed in a high humidity environment (100% R.H., 25°C) and then deagglomerated with the rig and the Diskhaler. The deagglomeration achieved with the rig and the inhaler were both reduced, showing that the rig can be used to test new powder formulations.

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Chapter 1

Introduction

Pharmaceutical aerosols provide a method of delivering drugs directly into the lungs, which has proved excellent for treating lung diseases such as asthma, however the delivery of drugs directly to the bloodstream through the lungs is an exciting possibility of inhaled medicines. Drugs that cannot be taken effectively orally such as insulin and vaccines, could be introduced into the bloodstream without the need for injection via needles. Although the field of inhaled pharmaceutical aerosol medicine is already thriving in its application to lung diseases, the possibilities for the field to expand beyond its current niche are numerous.

This work focused on the dispersion properties of micronized dry powder drugs and the ability of various forces to disperse agglomerates of these drug particles into their constituent particles. Also a deagglomeration apparatus, as a method of testing new formulations of dry powders, was designed and is presented in this thesis.

Hopefully the work contained in this thesis will be a helpful step to seeing pharmaceutical aerosols become a more prominent method of drug delivery, providing a better, safer and more efficient method of drug delivery to those that need it, thus increasing their quality of life.

1.1 Methods of Inhaled Pharmaceutical Aerosol Delivery

There are three main methods of producing pharmaceutical aerosols for inhalation:

1. Nebulizers. The drug is either dissolved or suspended colloidally in water, the water is then broken up into fine mist particles, with a jet or ultrasonic waves, which can be inhaled. An advantage of this method is the relative ease of formulating aqueous solutions. However, to disrupt the water into the fine mist of micron-sized particles relatively expensive delivery devices, (either a compressor or a ultrasonic nebulizer) that are typically too large and cumbersome to be portable, are required. New devices are being developed to address some of the portability issues[1] of nebulizers, however shelf life of drugs in aqueous solution is reduced for some drugs, providing further problems for portable nebulizer delivery systems.[2]

2. Pressurized Metered Dose Inhalers (pMDI). The most common method of aerosol delivery, these devices contain fine drug particles either dissolved or in suspension with a high vapor-pressure propellant. As the propellant is released through a metering valve, the propellant vaporizes and expands sending a bolus of small particles of the drug/propellant mixture out of the device. These devices are small, portable, versatile and inexpensive. One disadvantage of this device is coordination required to time intake breath with actuation of the inhaler, something that can be problematic with elderly and pediatric patients. Also the velocity of particles discharged from the inhaler can be quite fast, causing useless impaction in the throat. This problem can be mostly eliminated with the use of a spacer (an extension to the inhaler that gives the emitted

particles time to evaporate and slowdown), but this increases the size of the device reducing its portability.[1]

3. Dry Powder Inhalers (DPI). The DPI contains a small amount of micronized drug (diameter $< 5\mu$m) that is both entrained and deagglomerated by inhalation air flow. The DPI resembles the MDI in size and portability, but because it uses a very different method of generating aerosols it has quite different properties. Because the inhalation breath entrains the powder, the dry powder inhaler does not have the problem of timing the intake breath with actuation of the device. In addition the velocity of the powder exiting the inhaler is typically lower than that being emitted from a MDI, eliminating the need for a spacer. However the micronized powders have a tendency to agglomerate to form larger particles that are not respirable. Deagglomerating these particles can be difficult, leading to a multitude of designs for DPIs being developed over the years. It is of interest to note that the dry powder form of a drug may be significantly more stable than if it were stored in solution (as in a nebulizer formulation) or in a propellant suspension (as in a MDI), making the DPI an attractive method of aerosol delivery for such drugs.

1.2 Dry Powder Inhalers

As discussed in the previous section, DPIs have an important role to play in the delivery of pharmaceutical aerosols, however there are many problems to contend with when using micronized dry powders. Primarily, the problem of powder entrainment and deagglomeration must be addressed if a powder is to be used for inhalation. Entrainment of a powder can be aided by adding larger "carrier" particles (diameter $\sim 60\mu$m) but the issue of particle deagglomeration is still a problem.

There are many design criteria when designing a DPI (as discussed by Timsina *et al.*[3]) and to try to address these criteria many different DPIs have been designed. An important method of evaluating the DPIs is by their efficiency measured in terms of fine particle fraction (FPF). The fine particle fraction is defined as the mass fraction of particles deaggregated small enough to be inhaled. The cut off size for FPF is typically around 6 μm[4] and it may vary slightly depending on the device used to measure the size distribution (eg. the cut points of the Anderson impactor and of a multi-stage liquid impinger may be different). It is important to note that the FPF with a cut-off between 5-7 μm will likely over-estimate lung deposition,[5] and thus may not be the true efficiency of the inhaler, but measuring the FPF does provide a simple method of comparing inhalers. A typical FPF for a DPI is about 30%, although efficiencies as high as 50% and as low as 4% have been reported.[6] This disparity of FPF from one device to the next is evidence of the differences between inhalers.

Some inhalers presently on the market include (as described by Dunbar *et al.*[6]):

1. Spinhaler. The Spinhaler uses a capsule that is punctured prior to inhalation. The capsule sits on a small impeller that spins when flow is passed through the inhaler. The spinning and vibration of the capsules releases the powder through the holes punctured in the capsule. The spinning of the impeller then aids in the deagglomeration of the airborne powder. This device gives a low FPF of 4 - 12 %, likely due to the fact that carrier is not used in the Spinhaler drug formulation.[4,6]

2. Inhalator Ingelheim. The Inhalator, like the Spinhaler, uses a capsule for storage of the drug prior to inhalation. The capsule is pierced at either end and a portion of inhalation air flow is passed through these small

holes and entrains the drug in the air stream. This uptake, along with turbulence in the device probably cause most of the deaggregation of the powder. A FPF of 26% has been reported when using this device.[4,6]

3. Diskhaler. This device holds the drug in a multi-dose blister pack. The blisters are punctured and the powder falls into an uptake region. As a patient breathes through the inhaler, air through the blister pack entrains and deagglomerates the powder. After entrainment, the powder is exposed to a grid and turbulence which also aid in deagglomeration. The Diskhaler with Ventodisks are used in this thesis as a control, and a FPF achieved with this device was approx. 35% at 60 l/min (see Figure 3.1).

4. Turbuhaler. The Turbuhaler is a multi-dose inhaler that does not use blister-packs or capsules. The drug is not mixed with a larger carrier particle but is instead spheronized into small pellets, so total mass of powder per dose is much smaller than formulations with carrier particles. This allows it to hold 200 doses of drug in a reservoir, in each inhaler. The Turbuhaler dosing mechanism scraps a small amount of drug away from the drug reservoir and into conical holes in the dosing unit. Air flow during inhalation passes through these holes entraining and deaggregating the spheronized powder. The powder then passes through the mouth-piece which is designed to have a torturous path to further aid in the deagglomeration of the powder, via turbulence and mechanical impaction. FPF of 32 - 45 % have been reported with this inhaler.[4,6,7]

These are only a few of the types of dry powder inhalers in use, but they represent a cross-section of the devices and how the devices work. It is important to note that all the inhalers use many of the same forces to deagglomerate

the powder, and no inhaler uses only one method to deaggregate the powder. This combined with the fact that different inhalers use different dry powder formulations makes it difficult to know exactly why certain inhalers are more efficient at deaggregating dry powders than others.

1.3 New Dry Powder Aerosol Formulations

As the field of dry powder aerosols expands, new drug formulations are being developed more frequently. In some cases dry powders have the favorable property of allowing formulations that have an increased shelf-life. This is the case with dry powder lyophilized liposomes. Liposomes (a substance made from lipids) will encapsulate a drug and alter the pharmacokinetics of the drug, prolonging residence time in the lung, decreasing distribution to other sites and increasing the drug's ability to target cells such as macrophages.[2] The ability to test these liposome powders *in vitro* was a major motivation behind this thesis.

In vitro testing allows the measurement of the particle size distribution achieved with the powder, prior to clinical (*in vivo*) studies. If the FPF produced by *in vitro* testing is low, this problem can be addressed. If clinical trials are performed prior to *in vitro* testing and clinical effect is low, it is not known whether the FPF fraction is a problem or if the drug itself is ineffective.

1.4 Testing Pharmaceutical Dry Powder Aerosols

As can be seen in section 1.2, powders are tested in conjunction with inhalers. What may be overlooked is that the powders in the inhalers can be quite different. For example, Steckel *et al.*[4] discusses the possibilities why the Spinhaler produces a low fine particle fraction and concludes the problem to be with the powder (no carrier is included in the formulation tested). Yet to

be conclusive, the powders from the different inhales would have to be tested with a common device.

Since both the properties of the powder and the device independently are important, it would be useful to test the powder apart from the inhaler. Also, new dry powder drugs for inhalation are being developed not for use in any specific inhaler, but as an independent powder, yet to test these powders specific inhalers are used.[8–10] For these reasons, a device or method that tests the deaggregation of a powder, when exposed to forces similar to that produced with a DPI, would be a useful tool for testing dry powder pharmaceutical aerosols.

There are types of powder deagglomeration methods in the field of non-pharmaceutical dry powder aerosols, ranging from fluidized beds to high fluid energy aerodynamic methods.[11] However these methods focus on complete deagglomeration of powder into single particles, not on portability. A pharmaceutical DPI must by small, portable, and most use only the pressure of a patient's inhalation to disperse the powder. The few DPIs that do assist the deagglomeration of the drug particles using mechanical or aerodynamic means, are still limited in the amount of energy they can add because of the need for DPIs to be small and portable. Also the amount of powder tested with these devices is usually much larger than is dispersed with a DPI. Therefore most of these non-pharmaceutical dry powder aerosol deagglomeration devices use forces that would be much larger than that seen in a typical DPI. Thus using these devices to test a pharmaceutical aerosol powder would not give an accurate measurement of how well the powder would deagglomerate in a DPI.

Concessio *et al.* have examined several methods of testing pharmaceutical dry powder aerosols that do not require an inhaler.[12] They used methods such as: a RODOS powder disperser (Sympatec, GmbH, Germany), dynamic angle of repose measurements coupled with a novel chaos data analysis, and

detachment of powder from solid surfaces using a pendulum type impact force separation device. While all these methods are interesting in examining the properties of the powder, the methods are complex and special devices are needed. Also the results cannot be directly interpreted into a respirable fraction produced by a powder.

The need for a device designed specifically for testing of pharmaceutical dry powder inhaled aerosols without the use of an inhaler was seen and has been addressed by the work in this thesis.

1.5 Designing a Dry Powder Deagglomeration Rig

A device developed to deagglomerate new formulations of dry powder aerosols *in vitro* was designed with the following criteria in mind.

1. The device should be easy to load with a dose of powder. If an inhaler is used to test a powder, there is problem of getting the powder into the inhaler. Most DPI's use some form of sealed blister pack, or enclosed storage area to protect the powder. This makes it very difficult to insert a powder into the inhaler, after-market, for testing. There are a few inhalers (Spinhaler, Rotahaler, Inhalator Ingelheim) that store the powder in a capsule before use. These capsules are easier to load than other inhalers would be, however they still require a cumbersome loading method. And you have limited choices of which inhalers you can use to test the powder.

2. The device should use forces that are similar to those found in a DPI. A dry powder inhaler only disperses a small amount of powder per dose (< 25mg). A fluidized bed with glass beads that requires over a 1 gram of powder for proper operations would not be appropriate. Very high

pressure, high velocity flows may be unreasonable as well. The device's main goal is not the total deagglomeration of the powder, but to measure how well the powder will perform in a DPI.

3. The forces that deagglomerate the powder should be isolated as much as possible, unlike an inhaler, where the various forces occur simultaneously. A laboratory deagglomeration rig could be used to analyze how effective different forces are at deagglomerating the powder.

A rig was developed in the lab to satisfy these criteria as much as possible. The rig (discussed in more in section 2.3.1) entrains a small amount of powder from a tray inserted into an air flow. The powder then either is impacted on a grid (causing impaction deaggregation) or introduced into a highly turbulent region produced by a ring of impinging jets. The powder is passed directly into a Anderson inertial impactor, which allows an accurate measure of the FPF.

The turbulence producing jets were high velocity jets requiring a pressurized source perhaps violating point 2 of the above list. However, (as will be seen in the remainder of this thesis) the jets produced the turbulence that in turn deagglomerated the powder. The jets were not exposed directly to the powder. Also the rig did not deagglomerate the powder quite as well as the Diskhaler, so the deagglomerating force from the jet generated turbulence was of similar magnitude of that found in an inhaler, which is what the criteria require.

1.6 Summary of Thesis

Chapter 2 of this thesis goes into greater detail of the theory behind the deaggregation of dry powder aerosols, and discusses the experimental procedures

used to test the powders. Included in this is a description of the powder deagglomeration rig designed to test the powder.

Chapter 3 presents the results obtained from testing powders using the procedure outlined in chapter 2.

Chapter 4 discusses the experimental results shown in chapter 3, and some conclusions are drawn from these results.

Chapter 5 is a short summary of the work. Re-stating the main results of the thesis.

The included appendices are engineering drawings of the deagglomeration rig.

Chapter 2

Deagglomeration Theory, and Apparatus Design

2.1 Introduction

In this chapter the theory of deagglomeration of dry powder pharmaceutical aerosols will be discussed. This will lead into a discussion of the experimental apparatus and procedure. In this work two different experiments were designed and utilized; one is a method of testing varying forces on the deagglomeration of the dry powder aerosols, the second is a method of measuring the turbulence levels in the previously mentioned apparatus using laser Doppler velocimetry. Also a method of measuring the size distribution of freshly jet-milled particles before agglomeration in the collection chamber was designed.

2.2 Deagglomeration theory

2.2.1 Interparticulate adhesion forces

The adhesion forces between particles (due to Van der Waals forces, which is likely the main source of adhesion) is dependent on the following relationship:

$$F_{vdw} = \frac{\mathrm{A}}{6D^2}\frac{d_1 d_2}{d_1 + d_2} \tag{2.1}$$

Where:
A = Hamaker Constant (10^{-19}J, can vary from 0.001×10^{-19}J to 20×10^{-19}J)[13,14]
D = distance separating particles
$d_{1,2}$ = respective particle diameters

This relation is not very useful quantitatively, as it was theoretically derived for spherical particles (whereas most dry powder formulations would contain a variety of shapes), there may be several contact points, and there is a possibility of mechanical interlocking between the powders, all which deviate from the theory.[15] However it does show that, everything else being equal, the adhesion force is directly proportional to the diameter of the particles.

In contrast, the gravitational force on a particle is:

$$F = \frac{1}{6} g \pi d^3 \tag{2.2}$$

Where:

d = diameter of particle
g = acceleration of gravity

And a simplified aerodynamic lift or drag force would follow the formula:

$$F = \frac{1}{2} \mathrm{C}_{d,\ell}\, \rho U^2 \frac{\pi d^2}{4} \tag{2.3}$$

Where:
$\mathrm{C}_{d,\ell}$ = Coefficient of drag or lift
ρ = density of air
U = Velocity of air
d = diameter of particle

From both of these formulae, it can be seen that the deagglomerating and entrainment forces are proportional to either the diameter cubed (gravitational forces) or the diameter squared(aerodynamic forces). Thus as particle sizes become smaller the gravitational and aerodynamic forces are much reduced compared to the van der Waals force. Since the sizes of particles that are considered respirable are between 0.5 microns and 6 microns, the issue of deagglomeration becomes a real problem.

Before the powder can be inhaled it must be entrained in an inspiratory air stream. This can be difficult as indicated by the above discussion. The difficulty of entrainment can be overcome by adding lactose particles (as a carrier) with diameter on the order of 60 μm to the dry powder formulations. When mixed properly, the much smaller drug particles will adhere to the surface of the carrier particles. This allows the larger aerodynamic forces on the carrier particles to entrain the drug-carrier mixture. This is an adequate solution to the problem of entrainment, however the problem then becomes the removal of the the drug particles from the carrier.

2.2.2 Methods of Deagglomeration

2.2.2.1 Turbulence

It is commonly accepted that turbulence is an important part of powder deagglomeration in dry powder inhalers.[6,16,17] In a laminar flow field the relative velocity gradient on the scale of the particles size would be very small, probably not aiding in the deagglomeration of the powder. A turbulent flow field however, consists of very high velocity and pressure gradients, as well as fluctuating velocities, and these properties may aid in the removal of the drug particles from the carrier.

The turbulence could affect an entrained powder in several different ways as discussed by Finlay.[14] After some analysis Finlay uses the following equation as a method of determining the drag of a particle attached to a much larger particle in a turbulent flow as the particle undergoes a step change in turbulence level.

$$F_{drag} = C_d \frac{1}{2} \rho \frac{\pi d^2}{4} u^2 \tag{2.4}$$

Where:

C_d = Coefficient of drag $\simeq \frac{24}{Re_p}$
Re_p = drug particle Reynolds number $= \frac{ud}{\nu}$
ρ = density of air
u = turbulence velocity
d = diameter of drug particle

This formula is probably useful only for an order of magnitude analysis, however it does show how the turbulence velocity is an important factor in determining the deaggregation force on the powder. Note that the Re_p occurs in the denominator of Eqn. (2.4) implying that Eqn. (2.4) could be rewritten with Re_p included, thus reducing the power of u and d. However $C_d = \frac{24}{Re_p}$ only applies for low Reynolds numbers.[14,18] As the Re_p increases, $\frac{24}{Re_p}$ under estimates C_d. Therefore the proper power of u in Equation (2.4) is likely in range of 1 to 2.

The measurement of the turbulent velocity u (discussed in more detail in section 2.4) in (2.4) uses the RMS value of fluctuating velocity for u, i.e.

$$u = \sqrt{\sum_{j=1}^{n} u_j^2} \tag{2.5}$$

where:
u = turbulent velocity
u_j = j^th^ measurement of velocity in a series of n measurements at different times

For many turbulent flows the velocity of the most energetic eddies (turbulent velocity, u) is estimated very well by Eqn. (2.5).

2.2.2.2 Mechanical Impaction

When a carrier particle "carrying" drug particles collides with something large enough to drastically alter its course (e.g. a wall, or bars of a grid) it will undergo a deceleration. The drug particles on this decelerating carrier particle will then experience a force proportional to this deceleration as estimated by

the following equation:

$$F = \frac{\mathrm{m}_d v_c}{\Delta t} \tag{2.6}$$

where:
m_d = mass of drug particle
v_c = velocity of carrier prior to collision
Δt = time of collision

However, equation (2.6) does not take into account the direction the force occurs in. Only a portion of the small drug particles will experience this force in a direction that will actually remove them from the carrier particle.

If the powder is passed through a mesh (as it is in the deagglomeration rig) the powder will have a high probability of impacting on a mesh bar obstructing its path provided the carrier Stokes number (Stk_c) is > 10.[19,20] The carrier Stokes number is defined as:

$$\mathrm{Stk}_c = \frac{\mathrm{U}\rho_{particle} d_c^2}{18\mu \mathrm{D}} \tag{2.7}$$

where:
Stk_c = carrier particle Stokes number
U = velocity of carrier particle
$\rho_{particle}$ = density of carrier particle
d_c = diameter of carrier particle
μ = viscosity of air
D = Diameter of mesh bars

Therefore, if the carrier Stokes number is sufficiently high, the chance of a particle impacting on one of the mesh bars is equal to the area of the cross-section covered by the mesh bars. It is also of worth to note that the velocity of the carrier particles will not instantly be that of the entraining air flow, however the distance that the particle will travel before reaching the fluid velocity (X_{start}) is related to the Stokes number by the following:

$$X_{start} = \mathrm{Stk}_c \cdot \mathrm{D} = \frac{\mathrm{U}\rho_{particle} d_c^2}{18\mu} \tag{2.8}$$

2.3 Experimental Setup

To test the deagglomeration properties dry powder inhalation aerosols a rig was designed to expose the powders to turbulent forces and mechanical impaction forces separately. To measure what level of turbulence was generated by the powder deagglomeration rig, Laser Doppler Velocimetry was used. This is discussed in section 2.4.

The extent of deagglomeration of a powder is determined by measuring the size distribution of the powder after deagglomeration. This is expressed in terms of Fine Particle Fraction, and in this work it is defined as any powder deagglomerated to a size smaller than 5.6 μm. If the rig is used to test a non-commercial powder (ie. a powder formulated and milled in the lab, an example being the Liposome powders tested (see section 2.3.4)) then the size distribution of the powder just after milling is important. For example, if the powders was not milled to a size smaller than 5.6 μm then the powder will not appear to disperse using the deagglomeration rig. An experiment to determine the size distribution of a powder while milling is described in section 2.5.1.

2.3.1 Dry Powder Deagglomeration Rig

The ability to test the deagglomeration properties of pharmaceutical powders without using a particular inhaler is beneficial when designing new powders, also the forces involved in the deagglomeration of the powder are not easily quantifiable when using an inhaler. To address these issues a deagglomeration rig was designed as discussed in sections 1.4 and 1.5. The rig entrains a dose of powder into the air stream, and then after entrainment, it exposes the powder to either a controllable level of turbulence (Figure 2.1) or a mesh (Figure 2.2).

The rig is shown in Figure 2.3 (and engineering drawings are given in appendix A). The powder is placed on the *powder tray*, and then weighed

[illegible]

[illegible]

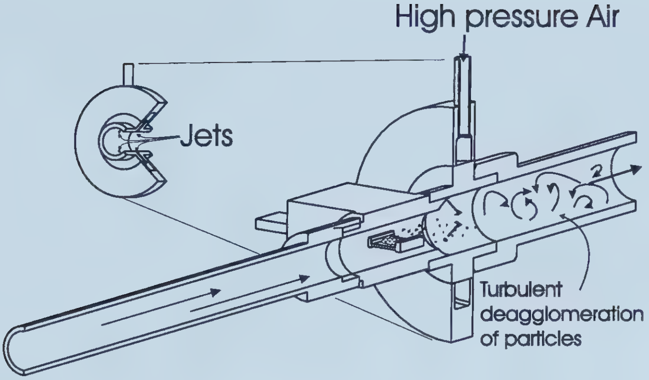

Figure 2.1: Powder being entrained and deagglomerated by turbulence

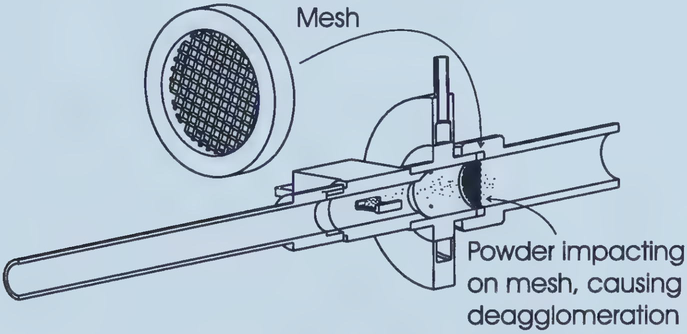

Figure 2.2: Powder being entrained and deagglomerated by impaction on bars of a mesh

using an analytical balance. The *powder tray* is then inserted into the flow, generated by a 1/3 HP vacuum pump, allowing the powder to be entrained. The entrained powder becomes exposed to turbulence created by the *jets*, and the effect of turbulence on powder deaggregation can be measured. The flow rate through the *jets* can be adjusted to control the level of turbulence. Alternatively (as shown in Figure 2.2) a mesh can be placed in the path of the powder causing the powder to impact on the mesh bars, thus testing the mechanical impaction method of deaggregation. The level of deaggregation

achieved is quantified by using an Anderson inertial cascade impactor.

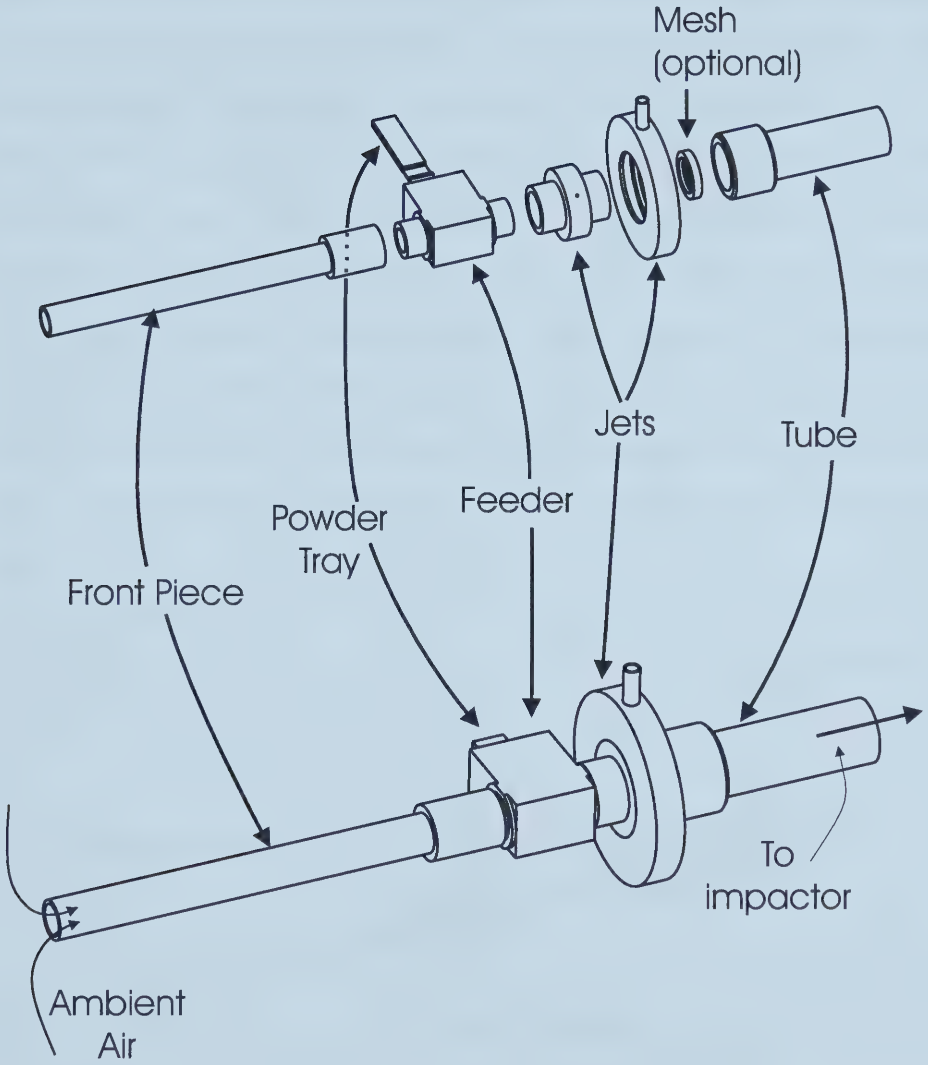

Figure 2.3: Schematic of powder deagglomeration apparatus

2.3.2 Deagglomeration Experimental Procedure

A Schematic of the experimental setup is shown in figure 2.4. From this figure it can be seen that the powder enters a non-viable Anderson Mark II inertial impactor with preseparator attached. The Anderson impactor measures the size distribution of the powder that enters it using inertial impaction. The plates of the impactor have been previously greased with Dow Corning 316 silicon spray grease, applied evenly across each plate twice with a 15 minute drying period after each application. This is done to eliminate the bounce of the powder particles off of the plates, which will give an incorrect size distribution.[21,22] Note that the preseparator is not sprayed with silicon grease. Also, the inlet of the Anderson impactor preseparator has been modified to allow a smoother entrance, and stage 7 has been removed to allow for a simpler assay.

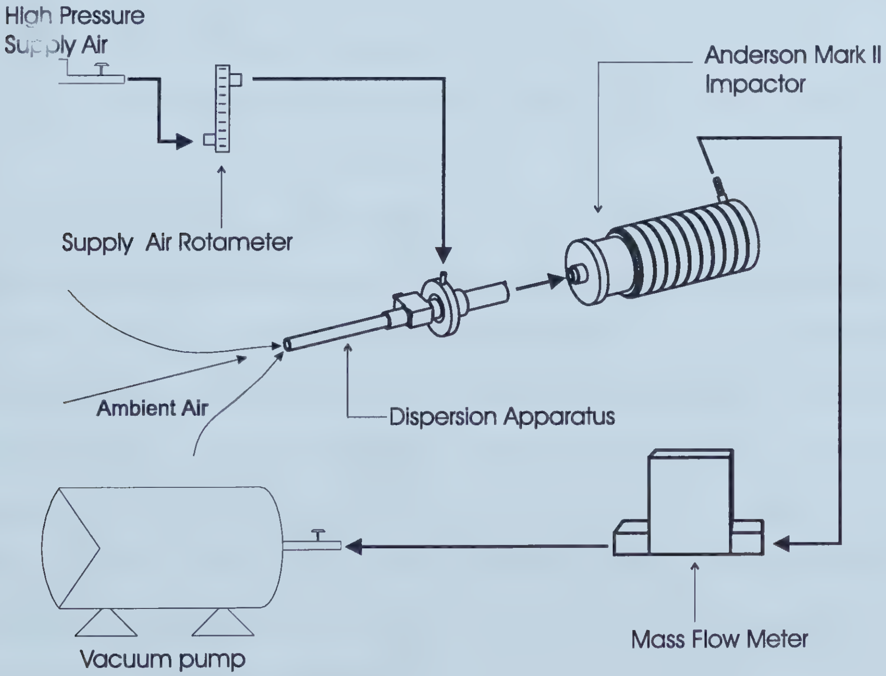

Figure 2.4: Experimental Setup

The impactor flow rate was set at 60 lpm using a mass flow meter (Matheson Gas Products, 0-100 lpm). This flow rate is not the recommended flow rate of 28.3 lpm (1 SCFM) normally used in the Anderson impactor, however due to need to somewhat simulate a human's inspiratory flow rate (because particle entrainment depends upon the higher velocities) the higher flow rate is used. The Mark II Anderson impactor has been recalibrated at 60 l/min,[23] and table 2.1 shows the cut points for the Anderson impactor when run at 60 l/min. Using this recalibration the size range of the powder impacted on each plate is known.

Plate number	Aerodynamic diameter (μm) cut point
0	5.6
1	4.3
2	3.4
3	2.0
4	1.1
5	0.51

Table 2.1: Cut points for Anderson inertial impactor when used at a flow rate of 60 lpm.

After the dispersion of the powder into the impactor is complete, the apparatus (excluding the *front piece*), the preseparator, the first impactor sieve, and all the impactor plates are assayed with between 3 to 10 ml (dependent on the piece) of water. The water is collected and in the case of liposomal drug formulations, methanol is added to disrupt the liposomes. The solution containing the powder from the plate is then analyzed with UV spectroscopy (using a Hewlett Packard Diode array Spectrophotometer, model 8452A) to determine the concentration of drug present. This gives an accurate measure of the drug deposited on each stage.

The recalibration of the Anderson Impactor shows that the cut point of first stage is 5.6μm, and it is commonly accepted that particles greater in

aerodynamic diameter than this are not small enough for respiration. Also it is important to know if the drug has become deagglomerated from the carrier particles, yet it is possible that an ungreased preseparator will allow some of the large particles to pass through[24] and land on stage 0 of the impactor. Stage 0 was greased, and thus should have a high collection efficiency. Therefore any drug measured on stages 1-5 can be considered as successfully deaggregated from the carrier particles. This result can be compared to the amount of powder weighed before the experiment to give a fine particle fraction (FPF).

If the *jets* are used for powder deagglomeration, a high pressure source is attached to the inlet of the *jets*. This air is metered using a 0-60 lpm rotameter (Omega products, model FL-3663C). Three different flow rates were used in these experiments: jet flow rates of 0, 20 ,40 lpm. Because the flow rate through the Anderson impactor had to be maintained at a constant 60 lpm, the flow rate upstream of the *jets* was less by an amount equal to the flow rate of the *jets*.

Two different meshes (placement shown in Figure 2.3) were used in the deagglomeration rig to test impaction deaggregation. The first (mesh 1) had a 54% obstruction coverage (wire diameter = 457.2 μm, gap diameter = 1143 μm), while the second (mesh 2) had an 84% obstruction coverage (wire diameter = 190.5 μm, gap diameter = 228.8 μm). As discussed in 2.2.2.2 the obstruction coverage should be equal to the percentage of powder impacting on the grid, thus exposing it to mechanical impaction forces.

2.3.3 Testing the GlaxoWelcome Diskhaler

In addition to testing the deagglomeration of powders when exposed to turbulence or impaction, the Diskhaler^{tm} (GlaxoWelcome) was tested in a similar fashion as a control. A sample picture of the Diskhaler is shown in Figure 2.5. The Diskhaler was attached to the *tube* (with the *jets, feeder, tray* and

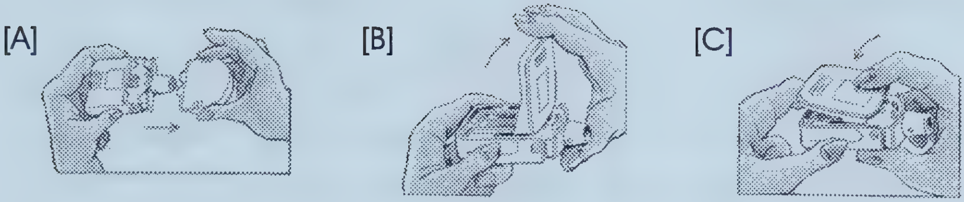

Figure 2.5: GlaxoWelcome Diskhaler^{tm}. [A] removing cover, [B] puncturing Ventodisk blister, [C] Ready for inhalation

frontpiece removed) with a special adapter that was form fitted to the outlet of the Diskhaler. Otherwise the experimental setup is very similar to that of the deagglomeration rig. A schematic of the deagglomeration tests using the Diskhaler is shown in Figure 2.6.

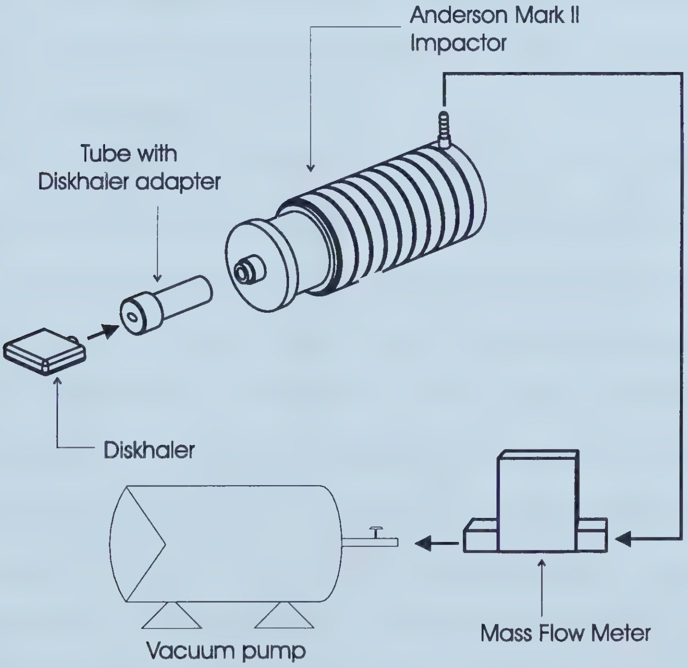

Figure 2.6: Experimental Setup with Diskhaler

2.3.4 Test Powders

For the majority of the deagglomeration experiments, powder from GlaxoWelcome Ventodisks (the disk-shaped blister packs used in the Diskhaler) was used. The powder contains carrier Lactose (estimated mean diameter 60 μm) and the drug Ventolin (Albuterol Sulfate) (estimated mean diameter 2.5 μm). This powder was chosen for several reasons: it is a well-known pharmaceutical powder, it is easy to remove from the Ventodisks, it is completely soluble in water (making the assay simpler), Albuterol Sulfate has large, linear UV absorbance over a sizable range, and it is inexpensive. To transfer the powder unto the tray, the Ventodisk is cut open and the powder is emptied into a vibrating spoon. The vibrating spoon is then used to transfer the powder unto the tray, which is weighed on an analytical balance. The tray is then inserted into the flow as per section 2.3.2.

To measure the effect of turbulence on powders of differing adhesion properties, the powder from the Ventodisk was exposed to humidity before being dispersed. Humidity generally increases adhesion in lactose powders,[14,25] and the Ventodisk powder is largely lactose, thus it was a simple way of altering the adhesion properties of the powder. The powders were stored in a humidity closet at 100% R.H. and 25°C for 15 minutes. Because the Diskhaler could not be used to test these powders if the powders were removed from the blister packs, the powder was left in the blisters, but a small hole (1mm diameter) was punched in the foil of each blister. This allowed the transfer of humidity from the ambient in the closet, to the powder in the blister pack.

To prevent humidity to effect the powders for the other tests, they were stored over desicant at room temperature.

In addition to Ventodisk powder, liposomal ciprofloxacin was also tested. These powders (like Ventolin) are an interactive mixture of fine particles (mean

diameter < 5 μm) and larger carrier particles. However the fine particles are a mixture of lyophilized liposomal encapsulated ciprofloxacin, and inhalation grade α-lactose milled with a Trost Gem-T jet-mill (discussed in greater detail in 2.5) to a respirable size (< 5 μm). Because the UV-active drug is encapsulated in the liposome, which is not water soluble, methanol is added to the solution washed off the impactor plate to disrupt the liposomes.

The lyophilized liposomal ciprofloxacin cake was prepared by Defense Research Establishment Sufield (DRES) for this research. The lyophilized cake that was milled for these experiments contained 0.888g lipids, 0.332g Ciprofloxacin encapsulated within the lipids, and 0.51g lactose. A portion of this cake was milled using the jet-mill and sized as per section 2.5.1. The milled powder was collected from the jet-mill and added to the α-lactose carrier particles (MMD $= 60\mu$m) at the ratio of 35.7mg of milled powder to 969.9mg of α-lactose. To ensure proper mixing of the milled powder and carrier particles, the two powders were mixed and sieved through a fine mesh (80 mesh) to aid fine particle break-up. This sieved mixture was shaken for 15 minutes using a modified shaker table. The mixture was sieved and shaken once more. The powder is then ready for dispersion.

2.4 Laser Doppler Velocimetry for Turbulence Measurements

Laser Doppler Velocimetry(LDV) is a method of measuring the velocities of particles passing through the intersecting point of two laser beams. As a particle passes through the fringe pattern formed by the intersecting beams, it scatters the light and allows the fringe pattern to be viewed off the direct path of the laser. Also, the particle shifts the frequency of the fringe pattern viewed in the scattered light, a phenomenon known as the "Doppler effect". This shift in the frequency is proportional to the velocity of the particle, thus measuring

the frequency of the scattered light allows a measurement of the velocity of the particle passing through the lasers. Thus LDV provides a non-intrusive, rapid method of measuring the instaneous velocity of a fluid at a point, provided the fluid is seeded with particles that follow the flow.

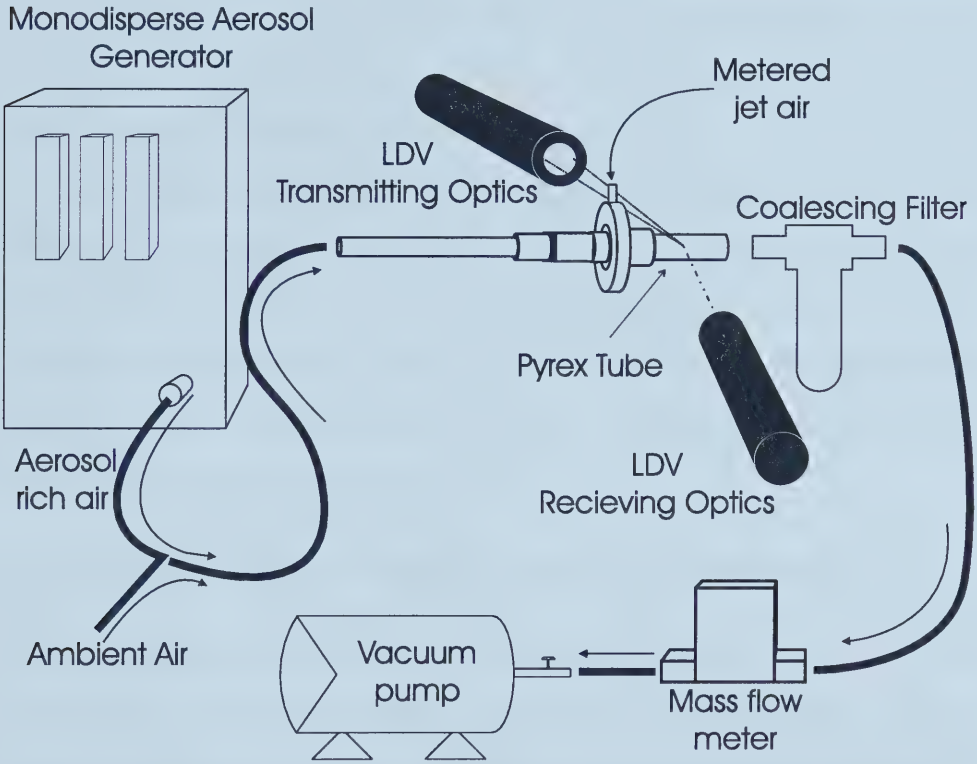

Figure 2.7: Experimental Setup For Laser Doppler Velocimetry

The experimental setup for the velocity measurements is shown in Figure 2.7. For the velocity measurements done in this work, a Laser Doppler Velocimeter from Dantec was used (He-Ne Laser @ 632.8 nm, manufactured 1995). A TSI monodisperse aerosol generator (model 3475) was used to generate a cloud of sufficiently small oil aerosol particles (mean diameter = 2.5 μm) needed for seeding the flow for the LDV. Because the aerosol generator only provides approximately 4lpm, at the outlet of the aerosol generator the aerosol rich air is mixed with room air to provide the needed flow rate (60 lpm

minus jet flow rate). This diluted aerosol is then passed through the deagglomeration rig and the Dantec LDV is used to determine the velocity of the aerosol downstream of the *jets* where the *tube* has been replaced by a pyrex tube to allow the receiving optics to view the light scattered by the passing aerosol particles. A coalescing filter then removes the oil aerosol from the air before it passes through the mass flow meter. The test was repeated for several different locations downstream of the jets.

The velocities downstream of the Diskhaler were measured in a very similar method. The deagglomeration rig was replaced with the inhaler which was directly attached to the pyrex tube. The inhaler was enclosed in a sealed container which was supplied with the mono-disperse aerosol, thus the inhaler's output is rich in aerosol particles allowing the turbulence generated by the inhaler to be measured with the LDV.

2.5 Jet-milling Pharmaceutical Powders

Jet-milling, also known as fluid energy pulverizing, is the reduction of particle size by particle-to-particle collisions due to particles being caught up in high velocity counter-flows. A diagram of the internal workings of the Trost Gem-T jet-mill (supplied by Plastomer Products) is shown in Figure 2.8. The powder to be milled is fed in through the inlet hopper, where the P-jet propels the powder into the mill. The O-jet then forces the powder into the clockwise pattern shown in Figure 2.8, this creates a point where the powder in the mill collides with the powder being forced into the mill by the P-jet. This collision causes particle fracture which reduces particle sizes. The clockwise swirl in the mill creates a centrifugal acceleration that allows only the smallest particles through the outlet, keeping the larger particles in the mill for more collisions. Thus, the mill will reduce a particular powder to reasonably repeatable size range, provided the pressures of the P-jet and O-jet do not change.

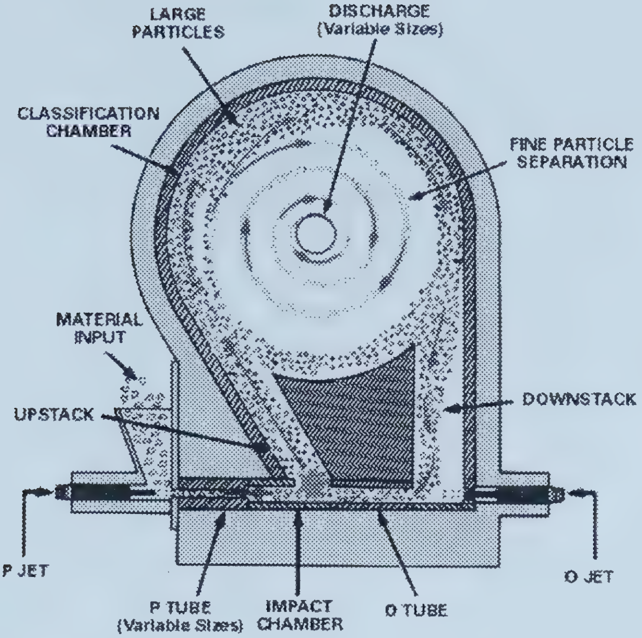

Figure 2.8: Internal workings of a Trost Gem-T Jet Mill

2.5.1 Sizing of Freshly Jet-Milled Pharmaceutical Powders

The powder exits the body of the mill through a small cyclone shown in Figure 2.9. The smaller particles follow the exiting air and are collected in the bag filter, while the larger milled particles are deposited in the collection container by impaction. This collection by impaction can, for specific powders, cause an agglomeration of the fine particles which leads to problems in dispersion and size measurement. However, the implementation of the following system allowed the particle sizes to be measured before the collection agglomeration occurs.

Figure 2.10 shows the standard configuration of the Gem-T jet mill and the altered configuration for the purposes of sizing the milled powders. The sizing device used was the Anderson Mark II impactor without the preseparator. To allow particle rich flow from the outlet of the mill into the impactor, a hole

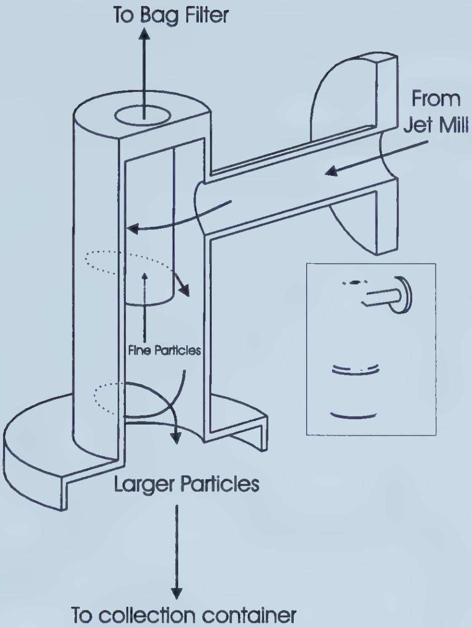

Figure 2.9: Cyclone outlet of Trost Gem-T Jet Mill

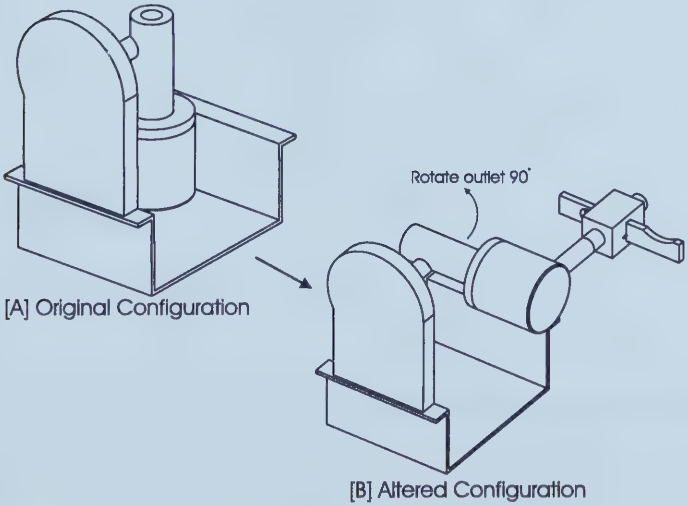

Figure 2.10: Jet Mill Configurations [A] Original Factory [B] Altered for particle sizing.

was cut in the collection container and a glass tube was glued to the container. An open, close, filter valve (OCF valve) was designed in order to control the amount of powder flowing from the jet mill into the impactor (to prevent

overloading of the impactor), and to insure the impactor flow rate remained a constant 28.3 lpm (standard operating flow rate for an Anderson Impactor) (see Figure 2.11). A schematic of the setup is shown in Figure 2.12.

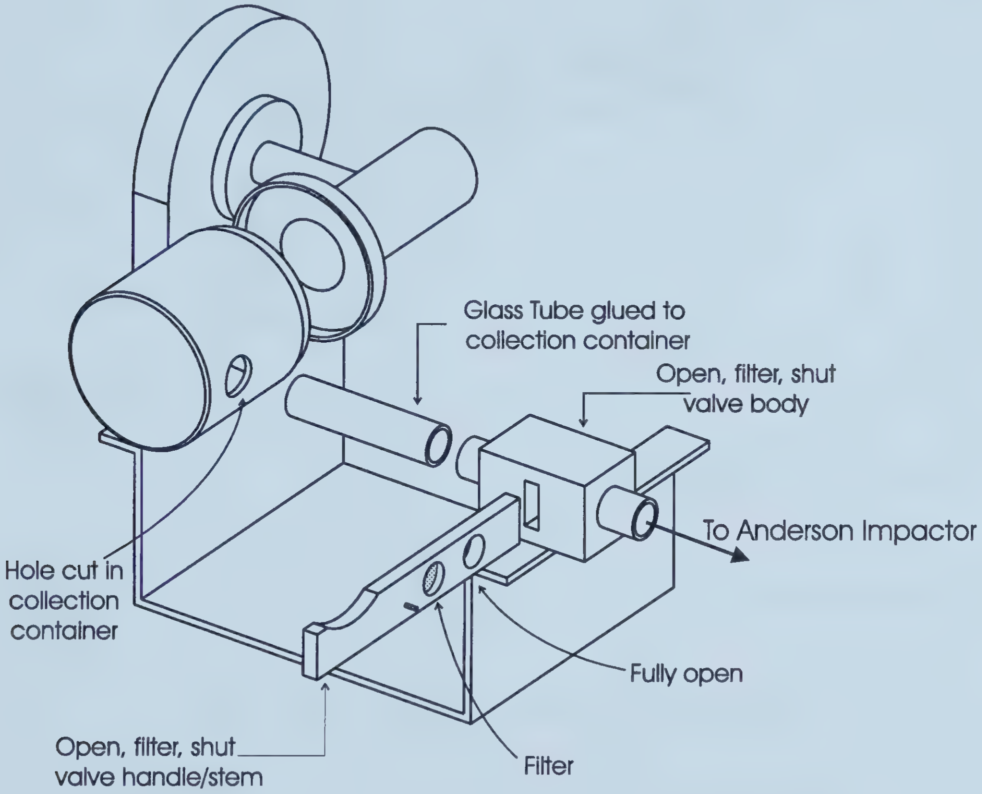

Figure 2.11: Jet Mill modifications.

The procedure for the sizing of jet milled particles with the Anderson impactor during milling is as follows:

1. Attach impactor to mill as shown in Figure 2.12
2. Ensure that flow rate through impactor is 28.3 lpm
3. Set OCF valve on filter
4. Turn on high pressure air and begin milling

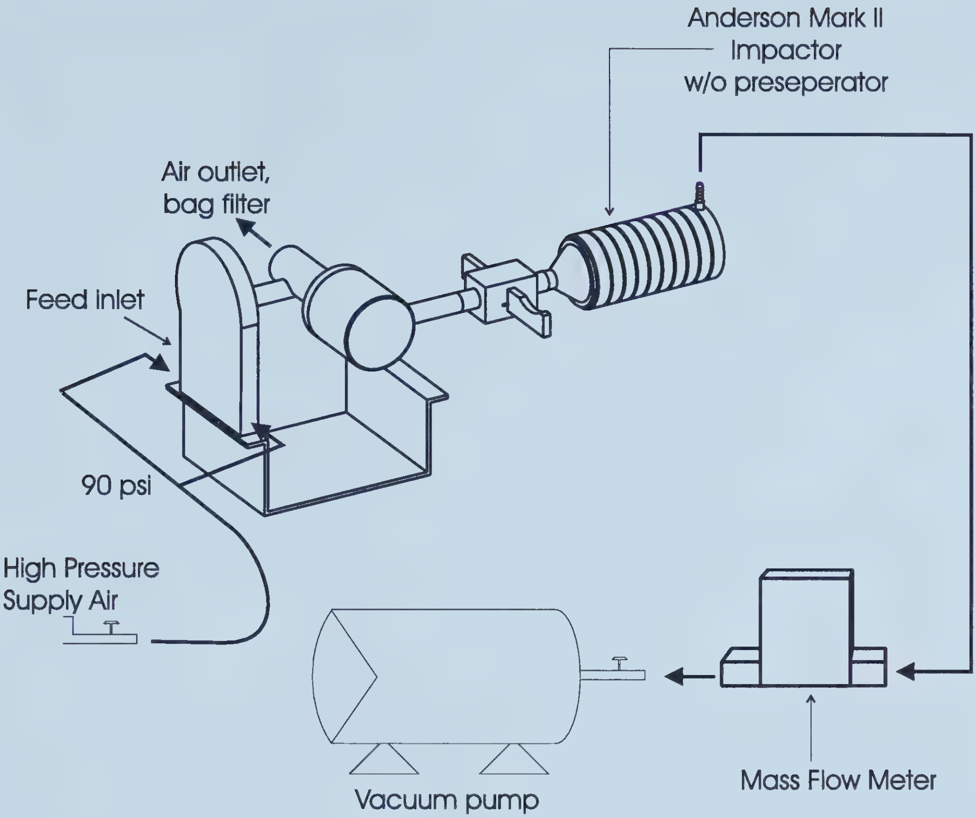

Figure 2.12: Jet Mill Particle Sizing Arrangement.

5. After powder begins to appear in the collection container, switch on vacuum pump
6. Quickly change OCF valve to open
7. Close valve after 5 - 10 seconds (depending on amount of powder in collection container) and switch off vacuum pump
8. Finish milling powder, and assay impactor

During normal operation of the jet mill some powder escapes from impacting in the collection container and escapes to the bag filter (shown in fig2.9). However, if the particles are sized, and the vacuum pump is operating to draw the milled powder into the Anderson impactor, there may be powder that

would normally go into the bag filter, entering the impactor. However according to the Trost manual,[26] only 5% to 10% of the mass of the milled particles are caught in the bag filter during a normal run.

Chapter 3

Experimental Results

3.1 Introduction

In this chapter the results of the experiments discussed in Chapter 2 will be given. The powder dispersion experiments were divided into 3 main groups: testing the deaggregating properties of turbulence by dispersing Ventodisk Powder in the deagglomeration rig with flow through the *jets*, testing mechanical impaction on the deaggregation of powders by inserting the wire meshes into the deagglomeration rig, and testing the effect of turbulent deaggregation on different types of powders (humidified Ventolin and jet-milled lyophilized liposomes). In addition to these tests the particle size distribution from the Diskhaler was analyzed as an independent source for which to compare the size distributions coming from the deagglomeration rig.

Turbulence measurements were also performed where the turbulence in the deagglomeration rig was measured at several locations downstream of the *jets* (all along the centerline of the *tube*). In addition, the turbulence downstream of the Diskhaler was measured (also along the centerline of the *tube*).

3.2 Effect of Turbulence on Deaggregation

All the experimental results shown in this section use the experimental setup discussed in 2.3.2. The experiments on turbulent deaggregation used the Ven-

tolin powder from the Ventodisks. The deaggregation was tested with the jet flow rate at 40, 20 and 0 l/min. Shown in table 3.1 is mass recovery of the tests. The recovery reflects the amount of drug recovered compared to the amount of Ventolin weighed before being dispersed. As table 3.1 shows the recovery for all the tests is quite reasonable, validating this method.

Jet flow rate (l/min)	Number of runs	Average Recovery (%)	Standard Deviation of Recovery (%)
40	5	105	8.5
20	6	106	9.1
0	8	100	5.9
Diskhaler	5	98	2.1

Table 3.1: Turbulent deaggregation experimental recovery

Figure 3.1 shows the FPF of the powder when deaggregated by differing flow rates through the jets. The error bars shown are the standard error $(\frac{\text{standard deviation}}{\sqrt{\text{number of runs}}})$. Figure 3.2 shows the cumulative mass distribution for powder in the respirable range (<5.6 μm, i.e. anything on plates 1 through 6 in the Anderson impactor, compared to the total amount found in the impactor not including preseparator).

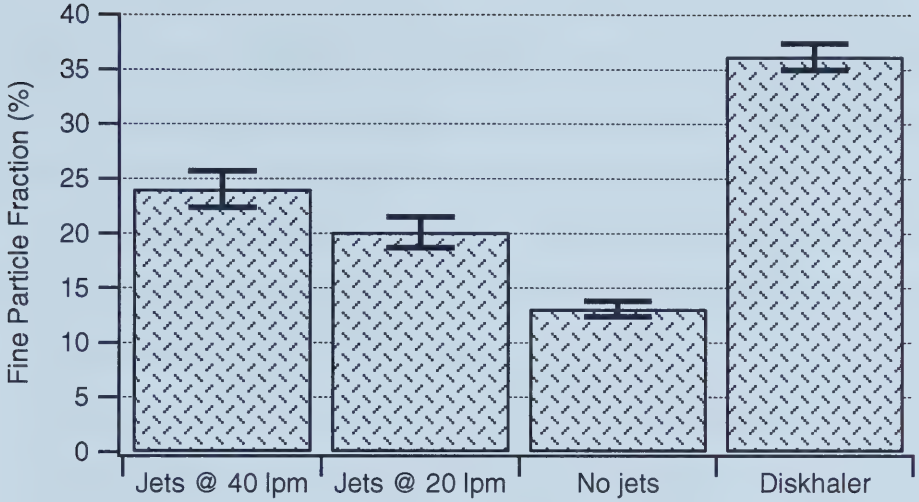

Figure 3.1: Deaggregation results of turbulence. Sorted by flow rate through the *jets*.

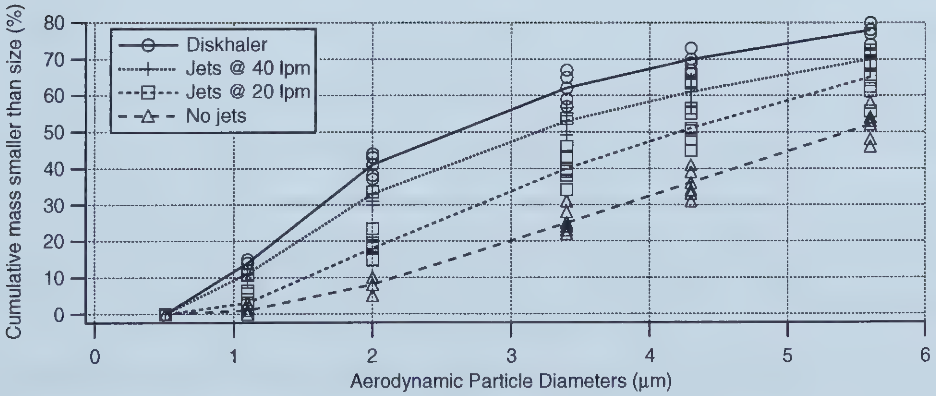

Figure 3.2: Cumulative size distribution of turbulence induced deaggregation. Lines show average results of the tests.

3.3 Effect of Mechanical Impaction on Deaggregation

To test mechanical impaction, a mesh was placed in the deagglomeration rig between the *jets* and the *tube* (as shown in Figure 2.3). Table 3.2 shows the number of runs and the recovery of the tests. As stated in section 2.3.2, mesh 1 had a 54% obstruction coverage (wire diameter = 457.2 μm, gap diameter = 1143 μm), while mesh 2 had an 84% obstruction coverage (wire diameter = 190.5 μm, gap diameter = 228.8 μm).

Mesh	Number of runs	Average Recovery (%)	Standard Deviation of Recovery (%)
1	4	106.7	4.4
2	5	107.5	6.9

Table 3.2: Recovery of mechanical impaction deaggregation experiments

The results of the experiments are shown in Figure 3.3. Also shown is the amount of drug that was assayed off the mesh following the experiment. This is important because the particles may have deaggregated due to the mesh but have become stuck to it and thus cannot count towards the FPF measured with the Anderson impactor. The amount of drug found on the grid shows that the powder is indeed impacting on the mesh, however according to 2.2.2.2 the amount of drug impacting the mesh should be 54% and 84% respectively. Therefore it is likely that there is more powder impacting on the grid than is found stuck on the grid after a run. It is important to note that the powder that remains on the grid, even if it was deagglomerated by the grid, will not be included in the FPF measured by the experiment, as the powder never entered the Anderson impactor.

Figure 3.4 shows the cumulative mass distribution for particles in the respirable range.

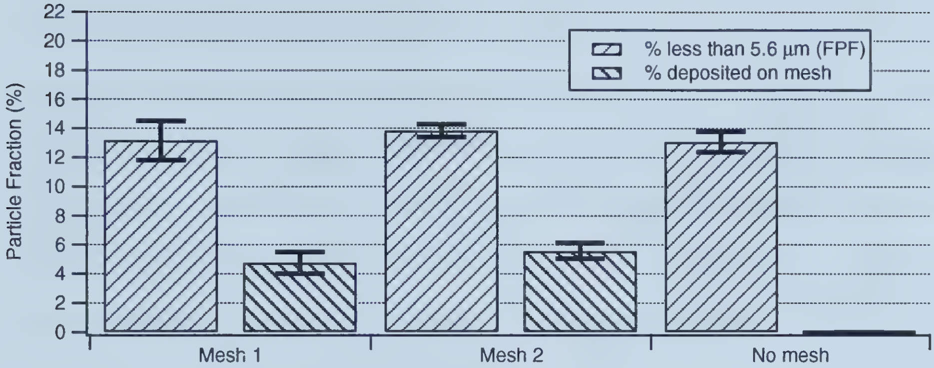

Figure 3.3: Deaggregation results of adding meshes for mechanical impaction. Included is the amount of drug deposited on mesh. Error bars shown are standard error.

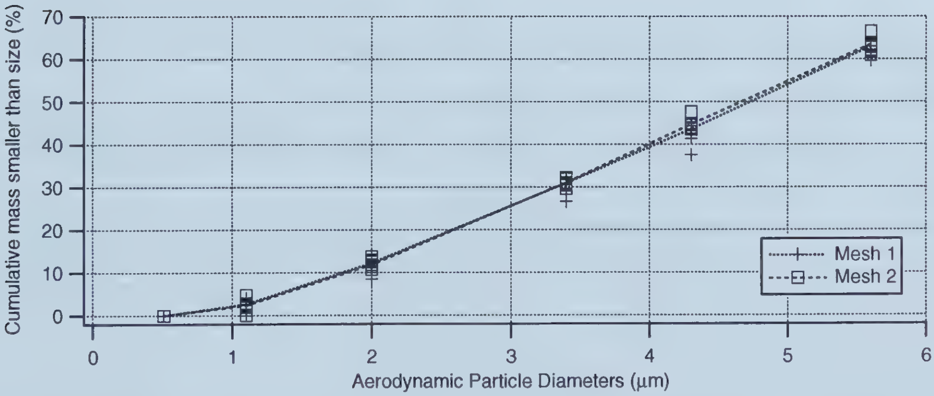

Figure 3.4: Cumulative size distribution for mechanical impaction

3.4 Using the Deagglomeration Rig to Test Different Powders

3.4.1 Humidified Powders

It is widely accepted that humidity (which leads to water uptake in the powder) will increase the adhesion forces in a powder such as the ventodisk powder, which is Ventolin mixed with Lactose.[25] Thus if humidified Ventolin is tested with the deagglomeration rig and with the Diskhaler, a relationship between the auto-adhesion properties of a powder (the ease with which a differing powders can be deagglomerated) and the FPF fraction achieved with the deagglomeration rig can be established. The powders tested were left in the Ventodisks but a small (1 mm) hole was punched in the blister packs and they were put in an environment of 100% R.H. and 25°C for 15 minutes. In Table 3.3 the runs and recovery of this study are shown. Figure 3.5 shows the results of these experiments, note that the results from Figure 3.1 are repeated to illustrate the effect of storing powders at high humidity by giving a direct comparison between FPF of the dry and humidified powders. Figure 3.6 shows cumulative mass distribution for these tests.

	Number of runs	Average Recovery (%)	Standard Deviation of Recovery (%)
Rig, Jets @ 40 l/min	5	104.9	1.5
Diskhaler	5	103	1.2

Table 3.3: Runs and recovery of dispersing powder stored at high humidity conditions

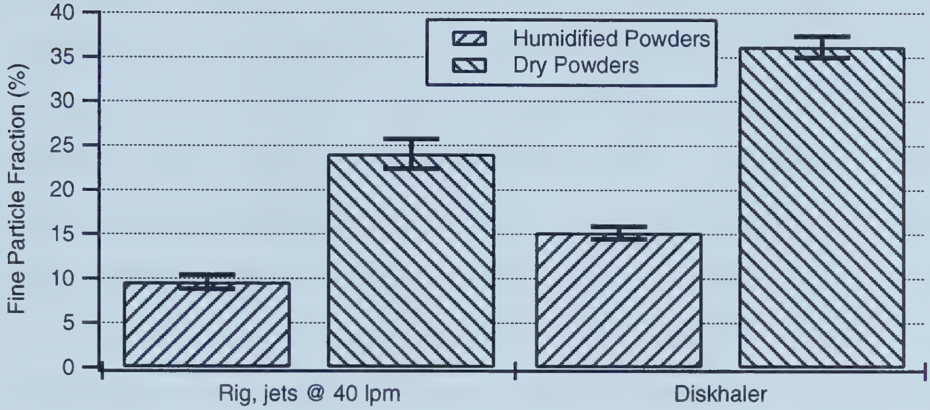

Figure 3.5: Fine particle fraction of powders stored @ 100% R.H. and 25°C compared to powders stored in dry conditions. Error bars shown are standard error.

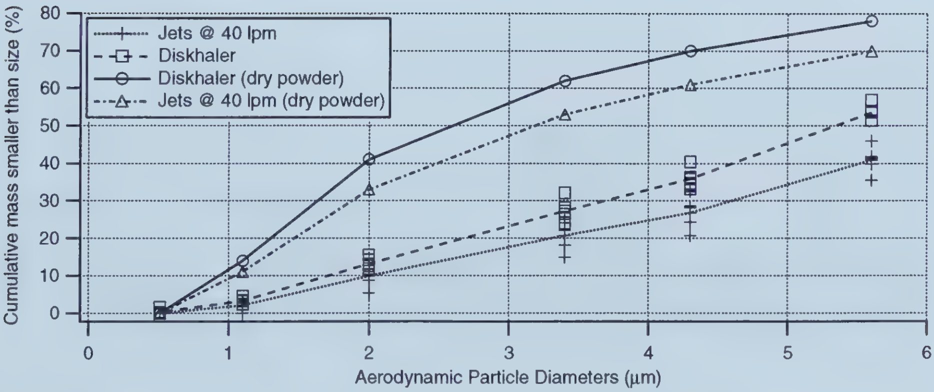

Figure 3.6: Cumulative size distribution of powders stored @ 100% R.H. and 25°C when deagglomerated with rig and Diskhaler. Average cumulative size distribution for powders stored in dry conditions are also shown.

3.4.2 Lyophilized Liposomes

The liposome powders were made using the process described in 2.3.4. Table 3.4 shows the runs and the recovery for the dispersion tests on the liposomal powders. Note that the recovery for the liposomal powders is not as good as the other tests, possibly making the results slightly less accurate. However the test was never refined because it was clear the powder did not deaggregate easily. Figure 3.7 shows the fine particle fraction of the liposomal powders when dispersed with the deagglomeration rig. The cumulative size distribution of the liposomal powder formulation is not shown because all the powder in the impactor was found on plates 0 or 1, thus the graph would not show any useful information (a single point at 5.6 μm).

	Number of runs	Average Recovery (%)	Standard Deviation of Recovery (%)
Jets @ 40 l/min	2	81	10
Jets @ 20 l/min	3	85	17
No Jets	3	79	4

Table 3.4: Liposome powders, runs and recovery

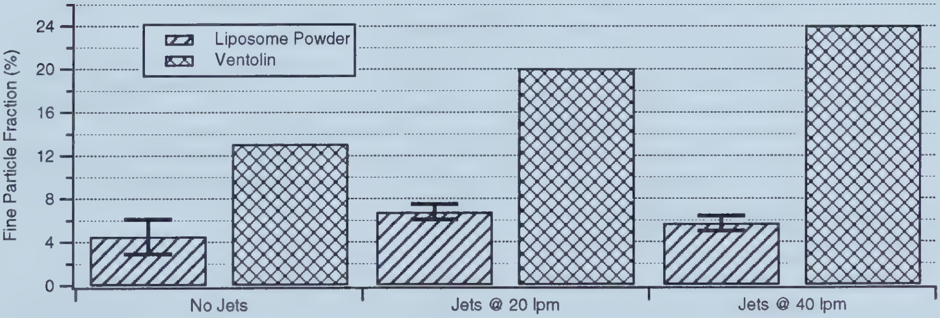

Figure 3.7: Fine particle fraction of liposomal ciprofloxacin when dispersed with deagglomeration rig. FPF for Ventolin is also included for reference.

3.5 Turbulence Measurements Using Laser Doppler Velocimetry

The turbulence measurements were performed on both the Diskhaler and the deagglomeration rig as discussed in 2.4. Because turbulence decays downstream from a production point, to compare the results of the tests some assumptions were made as to where the turbulence was being generated in the inhaler. As shown in Figure 3.8 the hole in the mouth piece of the inhaler was used as the origin of the turbulence. This is likely not exactly correct, but it allows us to compare the turbulence generated by the *jets* in the deagglomeration rig and that generated by the Diskhaler. Thus in Figure 3.9 the turbulent velocities are shown measured a distance downstream of either the centerline of the *jets* (in the rig) or the hole in the mouth piece (Diskhaler). All measurements are along the centerline of the tube.

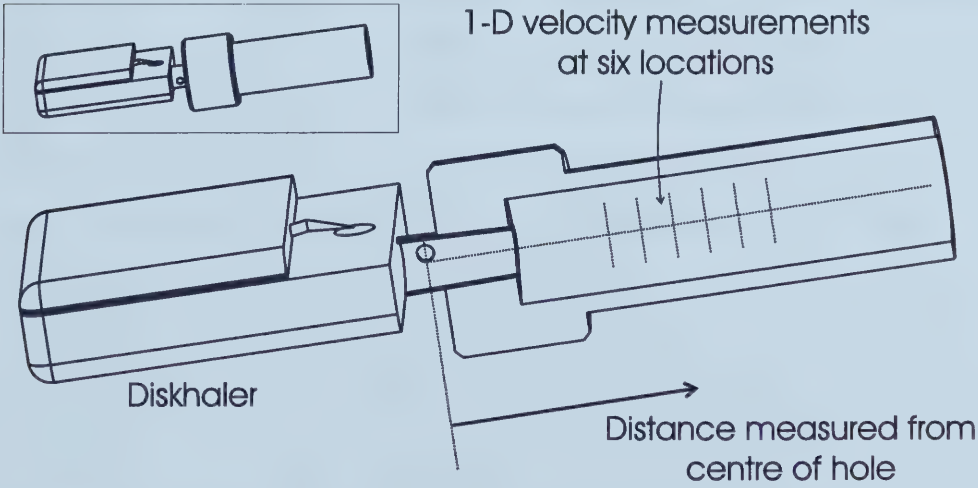

Figure 3.8: Measurement of velocities downstream of Diskhaler with LDV.

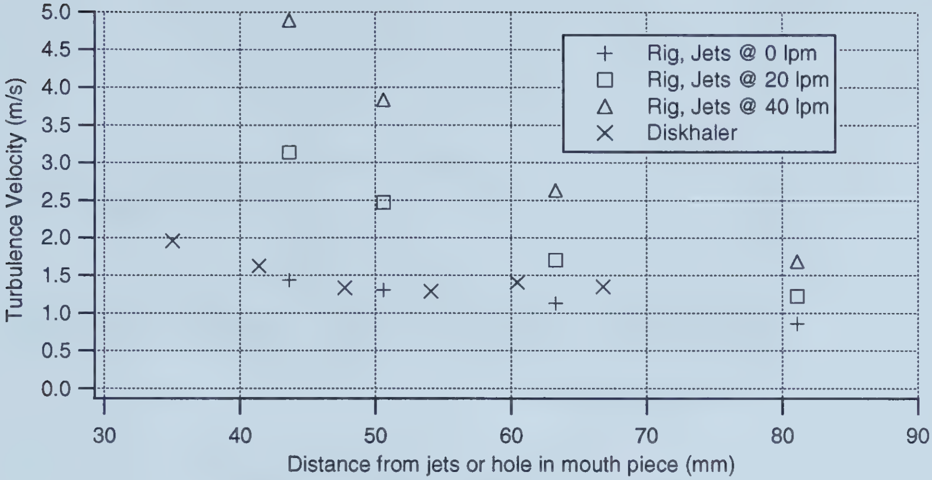

Figure 3.9: 1-D streamwise turbulent RMS velocities u along the centerline of the tube.

3.6 Sizing Particles From Jet Mill

Using the procedure outlined in section 2.5.1 the lyophilized liposomal ciprofloxacin (for which the deagglomeration results are shown in 3.4.2) was sized while being milled. Figure 3.10 shows the cumulative mass distribution in the Anderson impactor. The vacuum pump was run for 5 seconds with the OCF valve in the open position and the plates of the Anderson impactor were not overloaded.

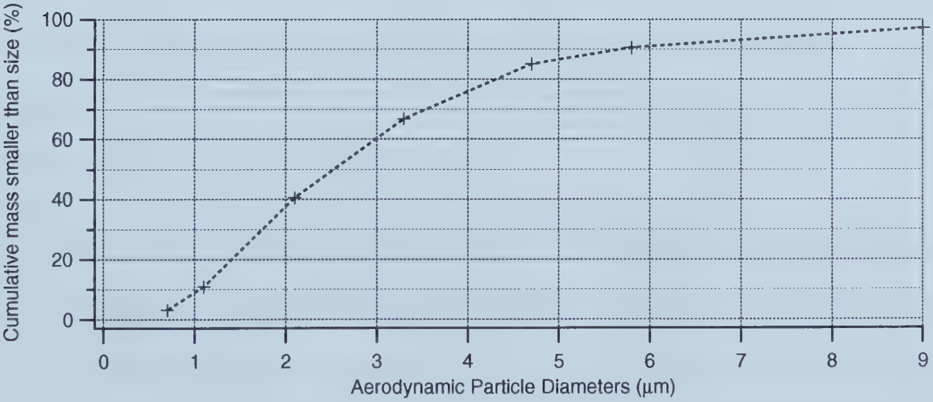

Figure 3.10: Cumulative mass distribution of jet milled liposomal powder. Sized during jet-milling

Chapter 4

Discussion and Conclusions

4.1 Turbulent Deaggregation

Figures 3.1 and 3.2 show that there is a definite correlation between the flow rate through the *jets* and the amount the Ventolin deaggregated from the carrier particles, while Figure 3.9 shows that as the *jet* flow rate is increased the fluctuating velocity increases(u from equation (2.4)). Therefore there is a correlation seen between the turbulence velocity and the deaggregation that occurs. Or, to put it another way, as the turbulence increases the deaggregating force increases.

Equation (2.4) predicts that the turbulent velocity has some bearing on the force causing the powder to deagglomerate, in that as the turbulence velocity increases, the deaggregating force will also increase. However an accurate prediction of the FPF due to a particular level of turbulence by analytical means is difficult for a variety of reasons:

1. The force between the drug and the carrier particles is generally unknown. In addition the force needs to be known for each particle as it likely varies from one particle to the next. Equation (2.1) provides this force between two *spherical* particles but does not include difficulties like multiple contact points, and mechanical interlocking.[15]

2. Particles will likely interact by colliding. This creates a multiple coupled system, as each particle may affect other particles, making the analysis complex.
3. The powder composition before dispersion must be completely known. This includes the size distribution of the drug and carrier particles. When using the powder from the Ventodisk this is not the case. However a powder created in the lab, such as the liposomal powder (if sized during milling), is much better defined.

The deagglomeration rig was designed to keep all variables the same while adjusting the flow rate through the jets. However, as the flow rate through the *jets* increases, the flow rate through the *frontpiece* and *feeder* is reduced by an equal amount. This means that the entrainment velocity (the flow rate through the *feeder*) changes with the changing *jet* flow rates. If the entrainment velocity has any part in the deagglomeration of the dry powder formulation then it is possibly altering the controlled portion of the test. It is likely that an increase in entrainment velocity would affect an increase in drug-carrier deagglomeration[14]. Since the entrainment velocity decreases with increasing *jet* flow, but FPF increases with increasing *jet* flow rate, it does not alter the conclusion that increasing the turbulent velocity increases particle deaggregation.

4.2 Mechanical Impaction

As is shown in Figure 3.3 the addition of the meshes do not significantly affect the FPF produced by the deagglomeration rig. In more detail, mesh 1 produced a FPF of 13.2%, mesh 2 produced a FPF of 13.8%, and in the case of no mesh the FPF was 13.1%. The increase in FPF does follow the increase in obstruction coverage, but the increase in FPF is insignificant. In

fact, the difference between the effect of mesh 1 and mesh 2 is not statistically significant ($p = 0.67$), neither is the difference in FPF between mesh 1 and no mesh ($p = 0.96$), or mesh 2 and no mesh ($p=0.465$) . Mesh 2 does have more deposition on itself (5.45%, error = 0.5%), which does make sense in that its obstruction coverage is 84% compared to the 54% of mesh 1 (average deposition of 4.75%, error = 0.7%). Yet again, this difference is not significant ($p = 0.35$).

From these results it can be seen that the meshes used did not have any effect on the FPF produced by the deagglomeration rig. If they do aid in the deagglomeration of the drug particles from the carrier particles, it is offset by the amount of drug that remains on the bars of the mesh. Equation (2.6) shows that the deaggregating force, generated by the impaction of a particle on the bars of the mesh, is proportional to the velocity the particle was traveling prior to its collision (v_c). In the deagglomeration rig, the average velocity of the flow prior to the mesh is 3.5 m/s, and using equation (2.8) an entrained carrier particle of 60 μm will reach this velocity in 3.9 cm, which is sufficiently before the mesh to ensure it is traveling at this speed prior to impact. The results of these experiments only apply to carrier particles traveling at this speed. Also to ensure impaction of a particle traveling into a bar of the mesh, the Stokes number (Stk) of the lactose carrier must be over 10.[19] Using equation (2.7) from 2.2.2.2, with d_c = 60 μm, U = 3.5 m/s, $\rho_{particle}$ = 1000 kg/m^3, $\mu = 1.8 \times 10^{-5} kg/m \cdot s$, D(width of a grid bar) = 457.2 μm (mesh 1) or 228.8 μm (mesh 2), the Stokes numbers are: Stk_c(mesh 1) = 52, Stk_c(mesh 2) = 245, both well over 10. Therefore, 54% of the powder impacting on mesh 1, and 84% of the powder impacting on mesh 2 is likely a good estimate.

From the above results it can be deduced that collision induced deaggregation (of Ventodisk powder) is not effective at velocities of 3.5 m/s or lower. These results are interesting, as screens and meshes are common among dry

powder inhalers. Of course, the velocity prior to impaction would be important when applying this result to specific dry powder inhalers. The Diskhaler for example, contains a mesh just downstream of the uptake region. If the flowrate through uptake region is 20 lpm (explained below), and the cross-sectional area just upstream of the gird is approximately 1 cm^2 then the velocity prior to impaction is 3.3 m/s, very similar to that tested in the rig, thus the grid in the Diskhaler probably does little to aid in deaggregation of of the dry powder.

4.3 Effectiveness of The Deagglomeration Rig Compared to the Diskhaler

As can be seen in Figure 3.1 the Diskhaler gives a much higher FPF when compared to the deagglomeration rig, even at the highest flow rate through the *jets*. Yet, the turbulence velocity of the flow shown in Figure 3.9 is much lower for the Diskhaler than it is for the deagglomeration rig with the flow rate through the *jets* at 40 l/min. Since it is clear that the turbulence does have an effect on the deaggregation of the powder (as discussed in 4.1), yet the FPF for the Diskhaler is higher than the rig while the turbulence measured is lower, then it can be asserted that the deaggregation from the Diskhaler is not entirely from turbulence. There is the possibility that the powder impacting on the grid in the entrainment region of the Diskhaler is causing the increased deaggregation. However, the data collected from from powder impacting on the meshes in the deagglomeration rig, does not support the theory that mechanical impaction plays this large of a roll in the deagglomeration of the Ventodisk powder.

Another explanation is that the relative velocities between the powder and entrainment air is large in the uptake region of the Diskhaler. Figure 4.1 is a sketch of the entrainment region of the Diskhaler. The Ventodisk blister is punctured, and the powder falls into the inhaler's uptake region. When air is

passed through the inhaler, it comes from two main areas: the holes on the sides of the mouth piece, and through the hole in Ventodisk blister.

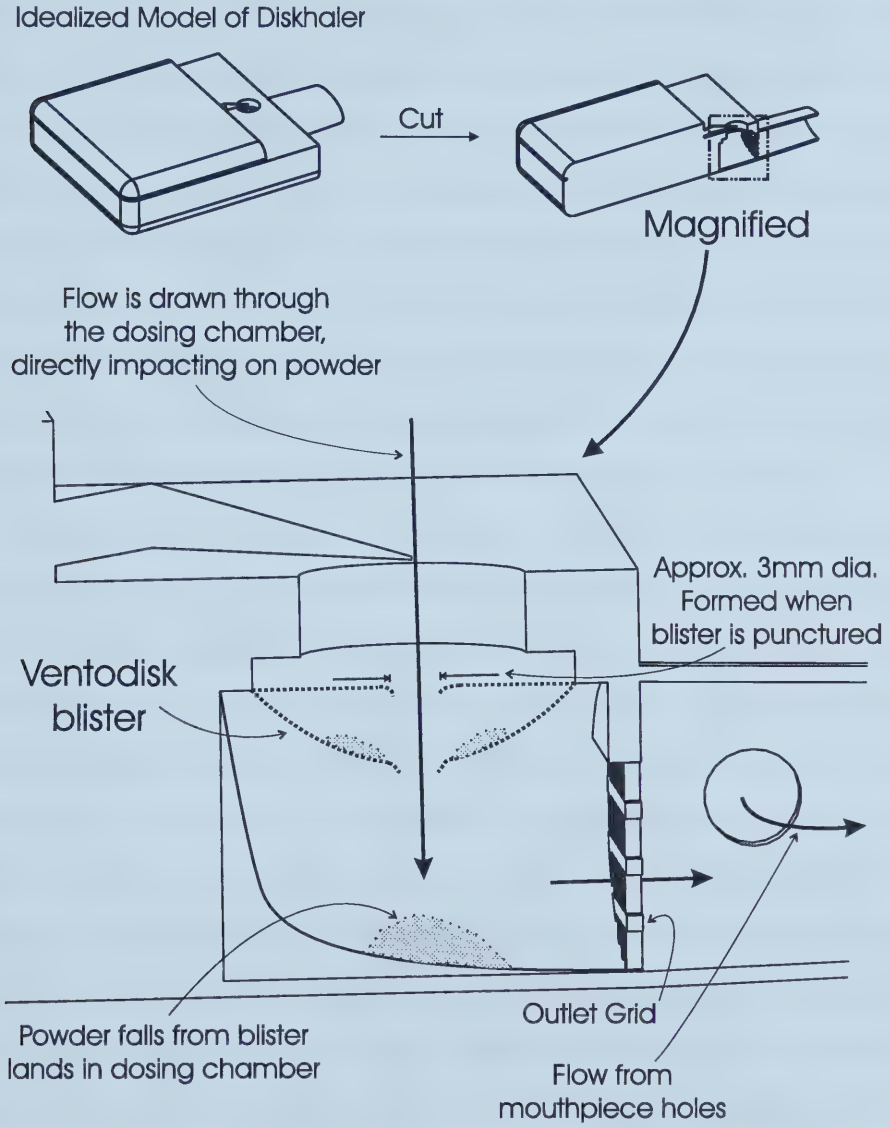

Figure 4.1: Close-up sketch of Diskhaler entrainment region. Powder falls from blister when punctured. When a flow rate is passed through the inhaler (intake of a breath, in-vitro with vacuum pump) a jet is formed from the holes punched in the blister. Also flow comes from the holes on either side of the mouth piece.

A jet is formed as the air passes through the hole in the blister. The velocity of this jet is unknown, but it it can be estimated by making the assumption that the resistance through the holes in the blister pack is similar the to resistance through the holes on either side of the mouth piece. If so, 1/3 of the air passes through the blister pack and the rest flows through the holes in the mouth piece. Of the flow rate of 60 l/min, 20 l/min is impinging directly on the powder in the uptake region of the inhaler. If the hole in the Ventodisk blister is 3 mm, the velocity of the jet would be 47 m/s. Whereas in the entrainment region of the deagglomeration rig the average velocity is 2.6 m/s (flow rate through entrainment region is 20 l/min when the *jets* are at 40 l/min and the diameter of the entrainment region is 12.7 mm).

This is a drastic difference in entrainment velocities, which may account for the discrepancy in FPF between the rig and inhaler. Also, the geometry of the two uptake regions are quite different. Figure 4.2 shows that the rig entrainment region is a flat plate in a cross flow, and the uptake of the carrier particles probably occurs by a shear layer lift or drag force forcing the powder off the tray and entraining it in the flow. In the Diskhaler however the jet through the blister pack impinges at a 90° angle to the surface the powder is laying on. This may cause the carrier particles not to follow the flow quite as fast, and exposing the drug particles on the surface to a greater drag force. This theory proposes that the physics behind the removal of drug particles from the carrier particles is the same for turbulent induced deaggregation as it is for uptake deaggregation, only that the relative velocity between the carrier particle and a nearby air flow is greater during uptake.

Like the turbulence induced deaggregation proposed in section 2.2.2.1 the deaggregation at uptake will probably obey equation (2.4) with the turbulence velocity replaced by an uptake velocity. This uptake velocity may be considered the relative velocity of the carrier particle velocity and the entrainment

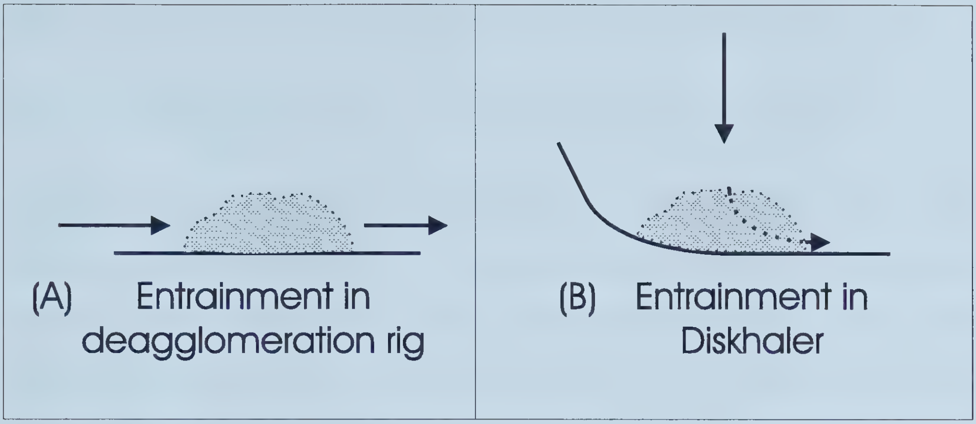

Figure 4.2: Uptake in (A) deagglomeration rig, and (B) Diskhaler. In the rig the surface the powder is entrained from (the *tray*) is parallel to the flow, in the Diskhaler the entraining air flow is at about a 90° angle to the surface the powder is laying on.

air velocity. An estimate of this velocity in the Diskhaler may be the velocity of jet impinging on the powder in the uptake region.

Turbulence is generally accepted to have a large effect on the deaggregation of dry powder pharmaceuticals in dry powder inhalers,[6,16,17] but the experiments done in this thesis show that although turbulence does play a roll, it is not the only, and possibly not the most important, method of deaggregation. This is a very interesting fact because it is possible that turbulence contributes to mouth/throat deposition. Perhaps the turbulence in DPI's should be reduced rather than increased and other methods of powder deaggregation should be examined, such as modifying the uptake region to increase entrainment velocity.

Increasing the efficiency of the rig is a very interesting problem that due to time constraints was never properly addressed. If there is significant deaggregation of the powder during entrainment uptake, perhaps the *feeder* and *powder tray* should be redesigned to increase the velocity of the entrainment fluid. Care should be taken to keep the rig in such a configuration so that the

deagglomerating forces can be isolated, making this a difficult task.

4.4 Using the Rig to Test Other Powders

In section 3.4 the results of using the deagglomeration rig to test powders other than the Ventodisk was shown. The results shown in Figure 3.5 illustrate that if the Ventodisk powder is stored in improper conditions the ability of the deagglomeration rig and the Diskhaler to deaggregate the powder is severely hampered. An important aspect of this is that the FPF from rig and Diskhaler correlate. If only the deagglomeration rig was used to disperse the humidified powder, the results would show that the powder is not suitable for inhalation, which is what dispersion with the Diskhaler has shown. This provides validation for using the deagglomeration rig as a method of testing powders without using a particular inhaler.

When the liposomal formulation was dispersed with rig (results shown in Figure 3.7) the FPF fraction varied from 4.5% to 6.8%, yet the amount of fine powder that was sized less than 5.6 μm was approximately 90% of the total milled (see Figure 3.10). This is a very low amount of powder that is deagglomerated from the carrier particles, even lower than that given by the Ventodisk powder when stored at high humidity (FPF = 9.6%). Therefore, this particular formulation of the lyophilized liposomal ciprofloxacin would not be a good formulation for inhalation.

Chapter 5

Summary

When making a new formulation of pharmaceutical dry powder aerosols for inhalation, *in vitro* testing provides important information as to how the drug will perform clinically. *In vitro* testing then is an important part of drug design and development. In this thesis, a device to test the deagglomeration properties of dry powder aerosol formulations was developed. This device can also be used to evaluate the effect of different types of forces on the deagglomeration of the dry powders. Specifically, the effects of turbulence and mechanical impaction were tested.

To evaluate the deagglomeration rig's effectiveness it was used to test the powder from the Glaxo Ventodisks and compared to the Glaxo Diskhaler. When turbulence from the rig was used to deagglomerate the powder, the FPF achieved at the highest flow rate from the *jets* (thus generating maximum turbulence) was 24%, whereas the FPF when there was no jet flow rate (much lower turbulence) was 13%, showing that turbulence indeed does have an effect on the deagglomeration of the dry powder aerosols. The Diskhaler however gave a higher FPF of 35%. When the turbulence velocity was measured for these different cases it was seen that the turbulence levels of the Diskhaler ($\sim$ 2 m/s) were much lower than that found when using the deagglomeration rig at maximum turbulence generation ($\sim$ 5 m/s). From this information it seems

that turbulence is not the only force in the inhaler that is deagglomerating the powder.

A conjecture was put forth that in the uptake region of the inhaler a significant amount deaggregation occurs. The uptake region in the inhaler is of markedly different design than that in the deagglomeration rig. The jet impinging directly on the powder during uptake may cause the additional deagglomeration seen with the inhaler when compared to the rig. The conclusion was that the uptake region of an inhaler may be a very important design aspect of an inhaler, and the turbulence generated may be less important than originally thought .

When a mesh was placed in the rig to aid in deaggregation of the powder, mechanical impaction deaggregation was tested. Two different meshes, of different obstruction coverage, were tested. The FPF when using either of the meshes was ~ 13.5%, very similar to the FPF of 13% when not using the meshes. It then appears that at the velocity used in the rig of 3.5 m/s (which is about the magnitude of the velocity in the Diskhaler) the deaggregation force due to mechanical impaction is not large enough to affect the fine particle fraction.

Ventodisk powder exposed to humidity will increase the auto-adhesion of the powder, decreasing the ease the powder deagglomerates to small particles. Ventodisks were placed in a high humidity environment (100% RH @ 25°C) and then deagglomerated with the rig and the Diskhaler. The FPF of the humidified powders when tested with the rig dropped from 24% to 10%, and dropped from 35% to 15% when tested with the Diskhaler. This illustrates that the rig can be used to predict the ability of a powder to deaggregate when placed in a inhaler. For example, a lyophilized liposome formulation was tested with the rig and a maximum FPF produced was ~ 6%, showing that this powder in its current formulation is not suitable for inhalation.

In conclusion, the powder deagglomeration rig designed was sucessful at providing useful information about the deaggregating forces that occur in dry powder inhalers, and even though the deagglomeration rig did not perform as well as an inhaler, it was shown that it could be used as method for testing pharmaceutical dry powders without using a specific inhaler.

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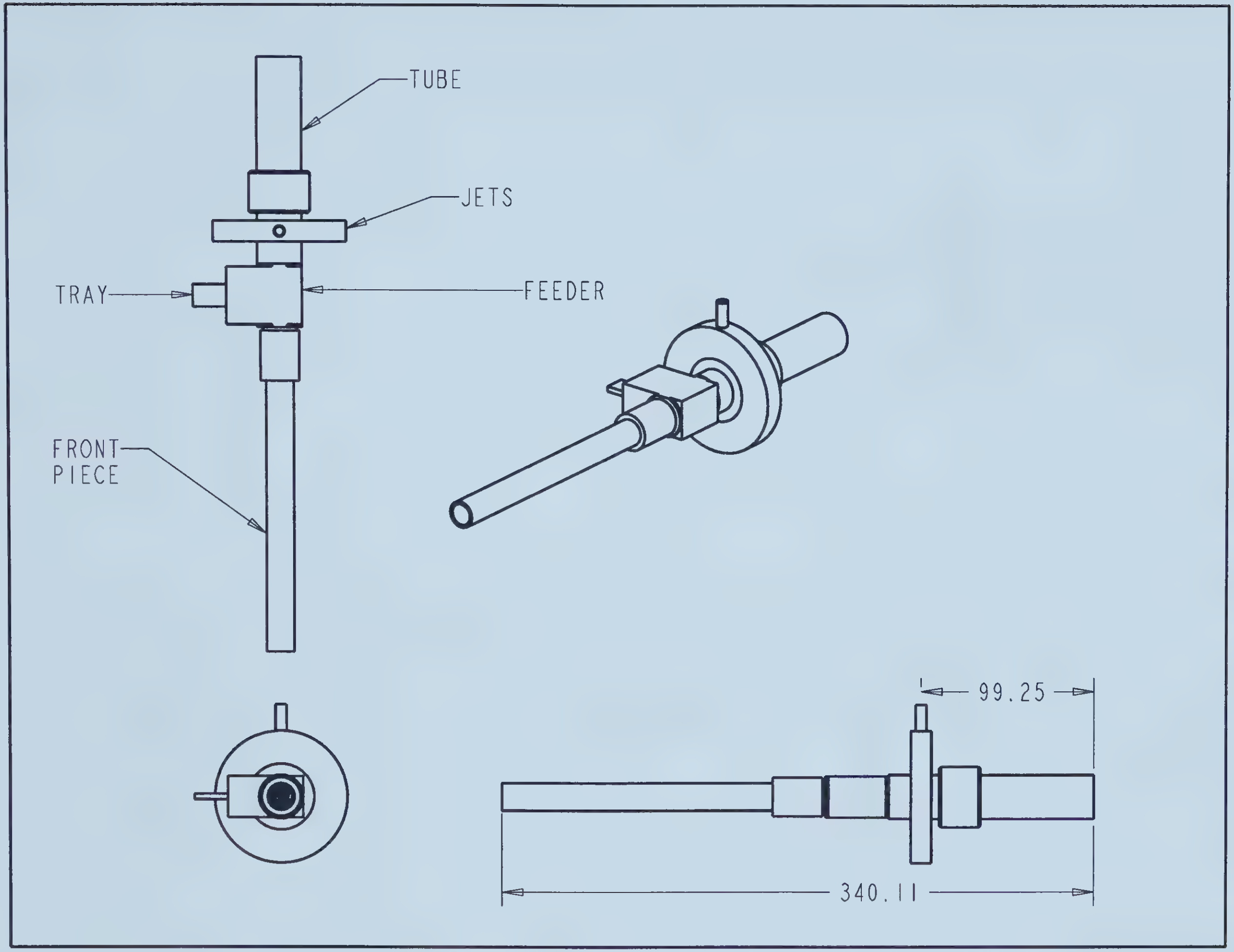
Appendix A

Engineering Drawings

NOTES:

1. All dimensions shown are in mm.
2. Unimportant dimensions are omitted (e.g. fillet radii)
3. All Parts were constructed with acrylic, except *tray*, which was constructed from aluminum.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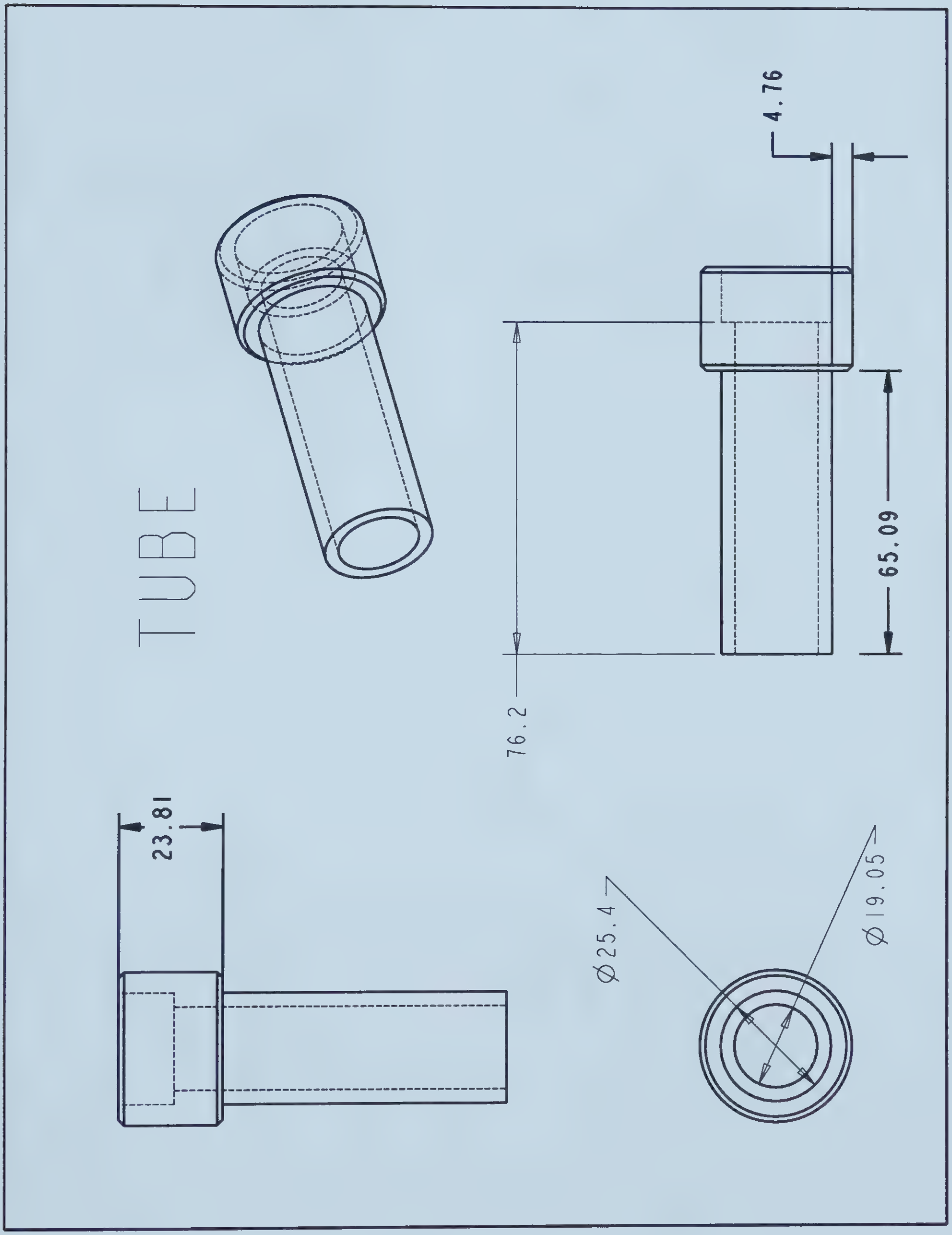
JETS
TRAY
FEEDER
FRONT PIECE
99.25
340.11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76.2
65.09
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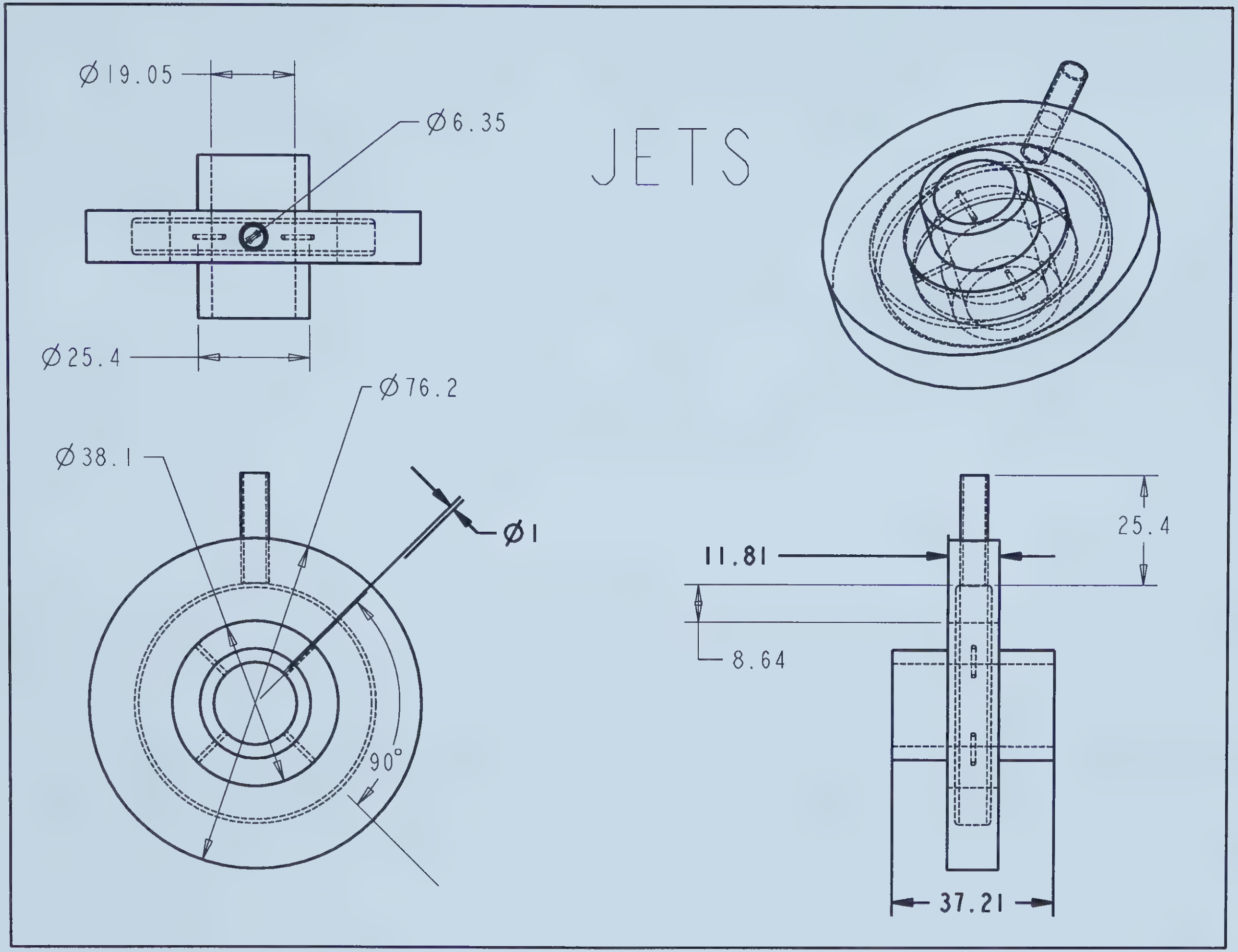
Ø25.4
Ø19.05


JETS
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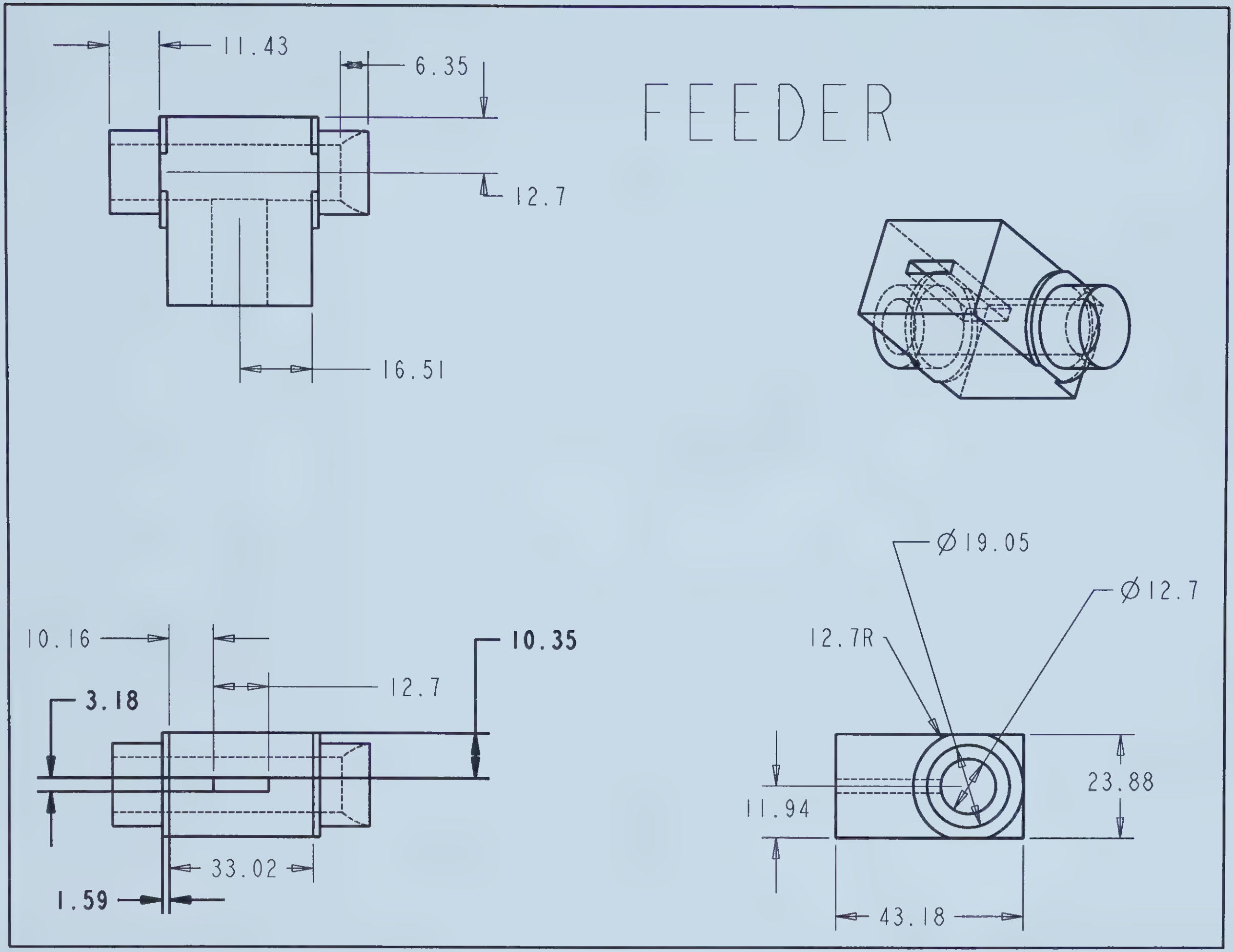
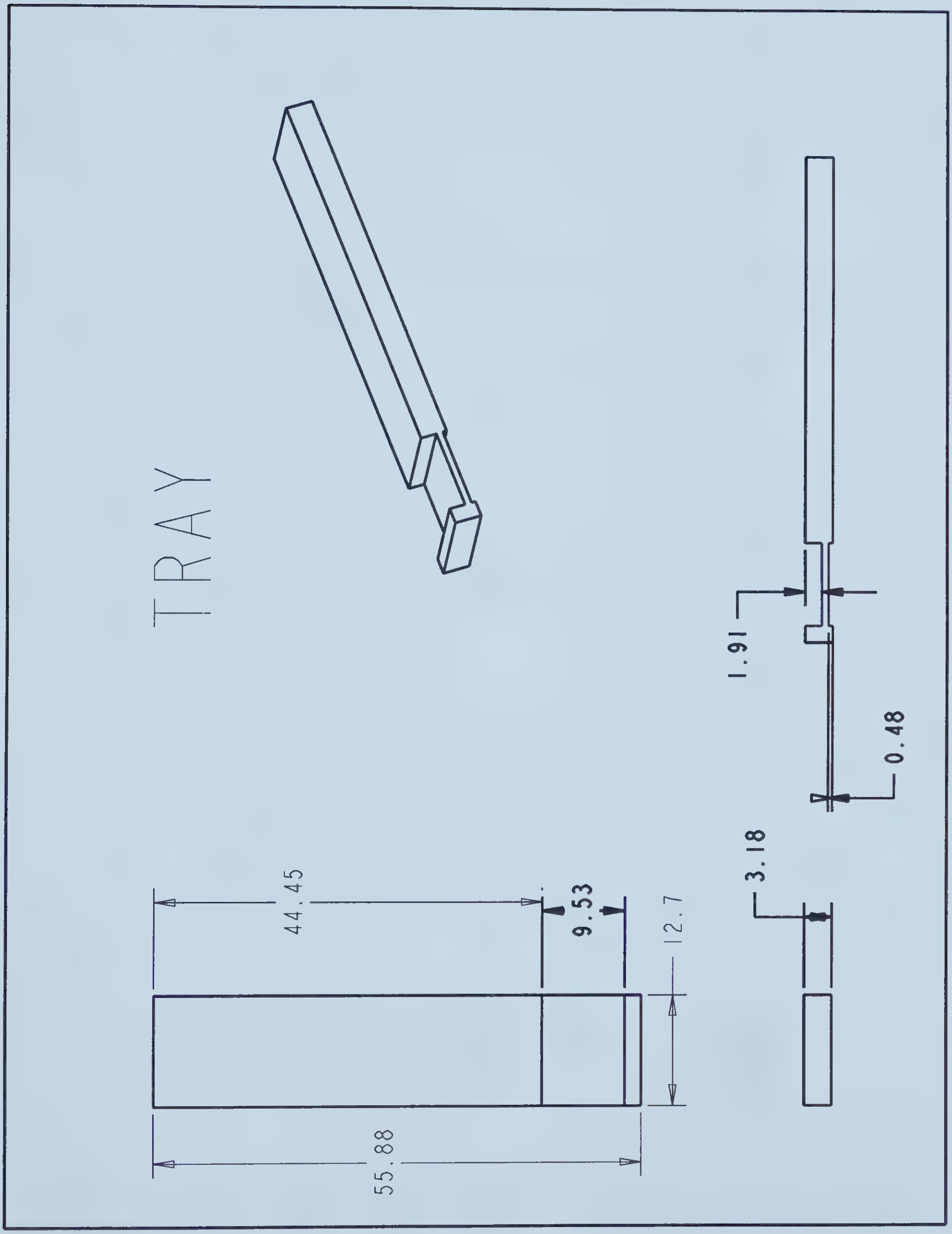
Ø25.4
Ø76.2
Ø38.1
Ø1
90°
11.81
25.4
8.64
37.21


FEEDER
11.43
6.35
12.7
16.51
10.16
3.18
12.7
10.35
33.02
1.59
Ø19.05
Ø12.7
12.7R
11.94
23.88
43.18


TRAY
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9.53
12.7
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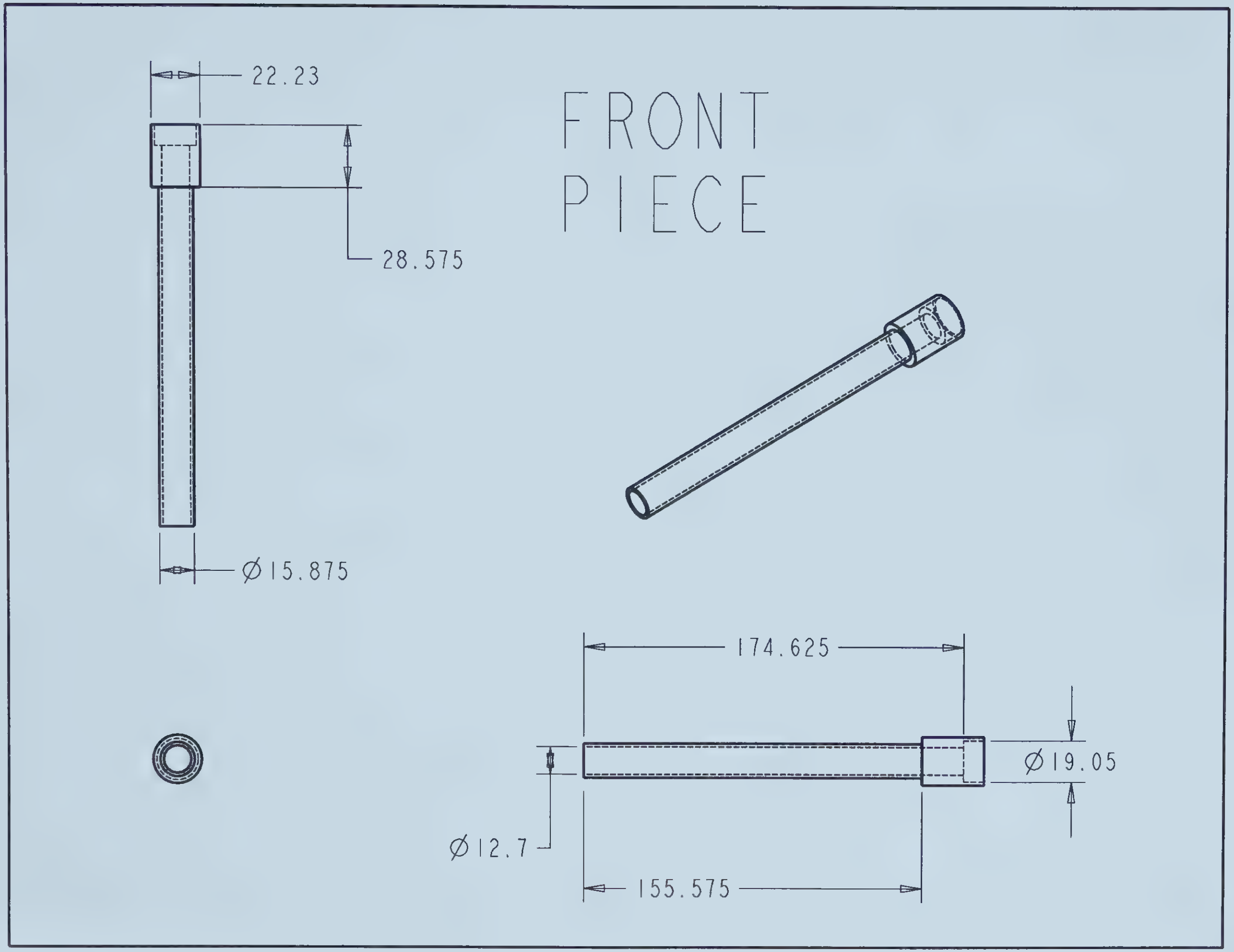
3.18
1.91
0.48


FRONT
PIECE
22.23
28.575
Ø15.875
174.625
Ø19.05
Ø12.7
155.575